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UNITED NATIONS

DIVISION OF NARCOTIC DRUGS

Geneva

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Evaluation of carisoprodol and phenyramidol for addictiveness

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Carisoprodol (N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate) is closely related to meprobamate in chemical structure (1). It is a centrally acting skeletal " muscle relaxant ", and is said to be particularly effective in releasing decerebrate rigidity (1). In experimental animals it produces high voltage, low frequency brainwave patterns and blocks electroencephalographic activation (1). It is unique in that it is ineffective as an analgesic by nociceptive or withdrawal reflex tests, but it is effective in counteracting pain produced by injection of silver nitrate into the joints of rats. That it may affect the central perception of certain forms of pain is suggested by behaviour of a dog subjected to painful stimulation of an extremity. The animal would withdraw the limb promptly in response to painful stimulus, but would not show dilatation of pupil usually noticed in response to pain (1). Evidence has also been provided that carisoprodol may elevate the pain threshold in man using (*a*) high frequency electronic stimulation to the tooth (Margolin, 2) and (*b*) an ultrasonic stimulus to induce deep, aching pain to the hand (Holliday & Dille, 2).

Phenyramidol (2-[Beta-hydroxyphenethylamino] pyridine) is also a CNS acting muscle relaxant, but in contradistinction to carisoprodol, it is effective as an analgesic by orthodox withdrawal reflex tests, and its potency in animals is comparable to that of codeine (12).

Both compounds are being marketed as muscle relaxants, effective in the relief of pain due to muscle spasms (11, 2). Since both compounds represent new structural departures for analgesics, experiments were carried out at the Addiction Research Center to ascertain if either possessed morphine-like addictive qualities in man.

General methods

The subjects used in these studies were healthy adult negro or white males serving sentences for violation of state or federal narcotic laws, who volunteered for the experiments. All were former opiate addicts. Since both drugs are being marketed for clinical use by the oral route, and since addicts would have difficulty extracting these drugs for injection from the inert ingredients with which they are mixed, they were evaluated orally only. The tests employed to ascertain addictiveness were:

1. Administration of single doses to non-tolerant subjects for the detection of morphine-like effects. This was evaluated by means of the single dose opiate questionnaires [patients' and observers' ratings (7)].

2. Twenty-four-hour substitution of these drugs for morphine in patients addicted to morphine, to ascertain their effectiveness in preventing symptoms of abstinence from morphine (6).

3. " Direct addiction ", which involves administration of these drugs in progressively increasing doses as tolerated for 18 days (5) and/or stabilization on the maximum dosage attained for an additional 36 to 43 days, and abrupt withdrawal of the drugs to ascertain whether physical dependence develops after either 18 or 54 days of chronic administration.

Other tests and specific details will be described under each experiment.

Part I. — Carisoprodol

1. *Effect of Single Oral Doses in Non-addicted Patients*

Methods. — Single doses of carisoprodol were administered orally in capsules to fasting, non-tolerant addicts at 8.30 a.m., and observations were carried out at hourly intervals for six hours, using the single-dose opiate questionnaires (patients' and observers' ratings).

Results. — Preliminary experiments indicated that doses below 1,000 mg induced no significant subjective effects, but with higher doses certain effects were demonstrated, as shown in table 1. It was not, however, until a dose of 2,000 mg

TABLE 1

Effects of single oral doses of carisoprodol (patient ratings)

Number of patients	Dose (mg)	Principal effects
4	1 050	3 – " blank " 1 – tranquillizer
4	1 200	3 – " blank " 1 – relaxed
4	1 600	2 – " blank " 1 – " dope " (2 of 6 responses)
5	2 000	2 – " dope " 3 – barbiturates
15	2 500	1 – " dope " (2 of 6 responses) 6 – barbiturates 3 – " blank " 1 – benzedrine 4 – miscellaneous 5 – sleepy

was given that effects were consistently observed. With 2,500 mg of carisoprodol, evaluated in 15 tests, only one of 15 patients identified it as being " dope " (opiate), and this patient identified it as such on only two of six observations. The predominate effects subjectively and objectively were similar to those of a barbiturate or alcohol, and not similar to those of an opiate. In contrast to patients intoxicated with barbiturates and alcohol, none of the patients who received large doses of carisoprodol were obstreperous, belligerent, silly or difficult to manage. One or two hours after 2,500 mg of carisoprodol, most of the subjects became quite sleepy, some profoundly so, and were difficult to arouse. They were somewhat confused when awakened, but did not show as much dysarthria as one might anticipate from an equivalent hypnotic dose of barbiturates. All patients thus affected, however, were moderately ataxic. These effects disappeared almost completely in six hours. Carisoprodol, even in the highest doses, did not induce pupillary constriction.

2. *Twenty-four-hour Substitution of Carisoprodol for Morphine*

Methods. — 3,600 to 4,800 mg of carisoprodol (divided into three equal oral doses) was substituted for morphine in 6 and 3 patients respectively. All patients receiving morphine were stabilized on 240 mg of subcutaneous morphine sulfate daily. The study was controlled in other tests, negatively, by substitution of a placebo for morphine, and positively, by continuing the customary dose of morphine in the same subjects. Observations for intensity of abstinence were made hourly from the 11th through the 24th hour of abstinence (6, 8). Since carisoprodol seemed to be barbiturate-like in many respects, the study was also controlled by substituting intramuscular pentobarbital in an average dose of 1.11 grammes divided among five doses, in another experiment using 11 other subjects. As in the preceding experiment, negative (placebo) and positive (morphine) control tests were made at weekly intervals in the same subjects.

The comparative effectiveness of the various agents in suppressing abstinence was evaluated by the paired *t*-test (3), using TAS values (total area scores) under the time-action curve for the 11 observations.

Results. — Carisoprodol partially but significantly ($P < 0.05$) suppressed symptoms of abstinence (figure 1), as tabulated by the hourly point score of Himmelsbach (8). Abstinence was

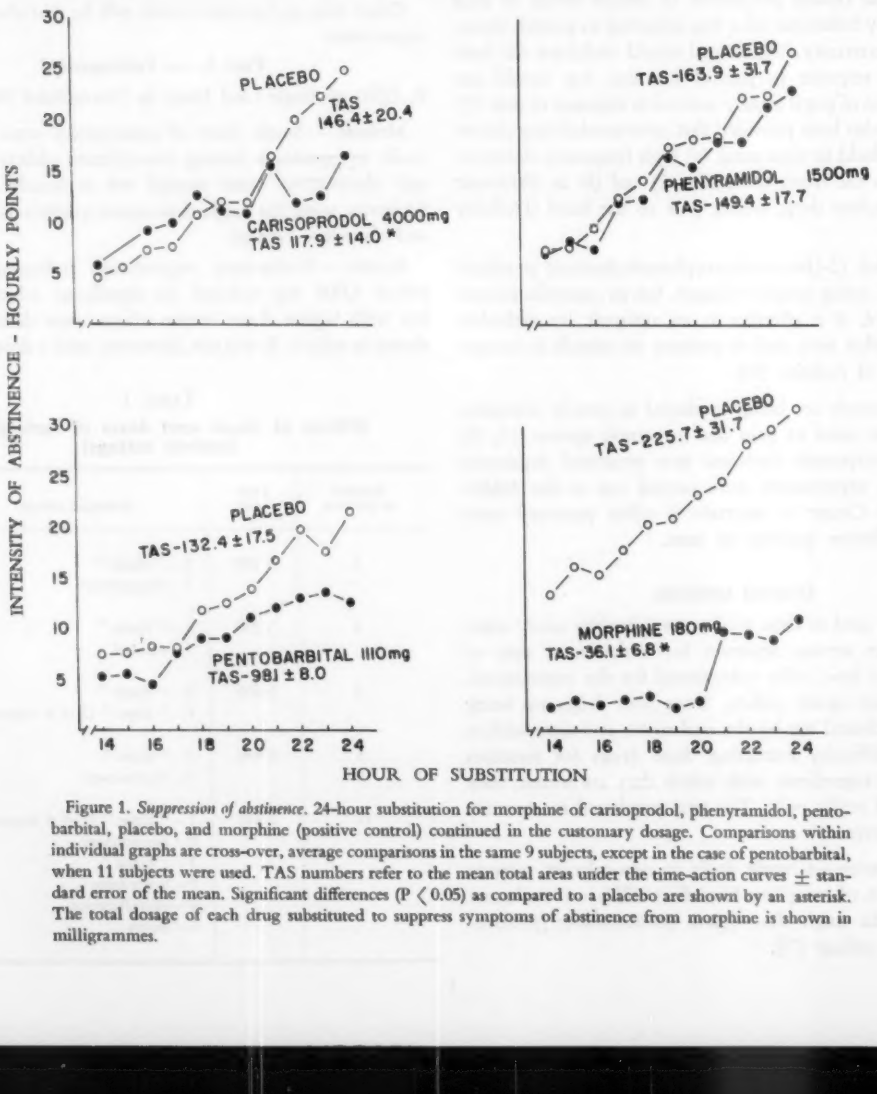

Figure 1. *Suppression of abstinence.* 24-hour substitution for morphine of carisoprodol, phenyramidol, pentobarbital, placebo, and morphine (positive control) continued in the customary dosage. Comparisons within individual graphs are cross-over, average comparisons in the same 9 subjects, except in the case of pentobarbital, when 11 subjects were used. TAS numbers refer to the mean total areas under the time-action curves ± standard error of the mean. Significant differences ($P < 0.05$) as compared to a placebo are shown by an asterisk. The total dosage of each drug substituted to suppress symptoms of abstinence from morphine is shown in milligrammes.

also suppressed partially by pentobarbital (figure 1), but not to a statistically significant degree ($P < .1$ and $> .05$). The 3 patients receiving the 4,800-mg substitution dose of carisoprodol were quite sedated and somewhat difficult to arouse, but showed only a slight degree of dysarthria and ataxia. All patients who received pentobarbital were sedated and showed a slight to moderate degree of ataxia and dysarthria; certain subjects were confused.

3. *Direct Addiction to Carisoprodol*

Methods. — Five non-tolerant subjects were used in a "single-blind" test — i.e., patients but not observers were unaware of the nature and schedule of medication. Starch placebos and carisoprodol powder were prepared in identically appearing capsules, and all medication was divided equally among four doses daily. All patients initially received placebo capsules for 12 days, 4 received carisoprodol for 18 days and one for 54 days. Carisoprodol was withdrawn abruptly and replaced by identically appearing capsules. The initial daily dose of carisoprodol was 1,200 mg; this was increased at a rate of 200 mg daily for 16 days to a daily dose of 4,200 mg, and then by 300 mg on the 17th and 18th days, attaining a daily dose of 4,800 mg. The patient receiving carisoprodol for 54 days received 4,800 mg daily from the 18th to the 54th day.

Observations were made three times daily throughout the experiment, and the degree of abstinence was calculated by the daily point scores of Kolb & Himmelsbach (10). In one patient, evidence of physical dependence was also evaluated (5) by administering 2 mg of nalorphine subcutaneously on the 44th day, and 5 mg on the 48th day of carisoprodol administration. Throughout the test, patients and aides independently completed a chronic dosage opiate questionnaire (7) at 7 p.m. daily. Clinical toxicity was evaluated by observations and by laboratory tests made prior to drug administration and repeated at bi-weekly intervals, when carisoprodol was administered, as follows: routine analyses of urine, red and white blood cell counts, hemoglobin content, hematocrit and liver function tests (thymol turbidity cephalin flocculation and evidence of bilirubin in the urine). An electrocardiogram was made on each patient while receiving placebos, and again after a high dosage of carisoprodol had been reached — i.e., 4,200 or 4,800 mg daily.

EEGs were obtained using an eight-channel resistance capacitance coupled Grass apparatus. Using needle electrodes, one bi-polar and three mono-polar tracings (linked and grounded) were obtained from frontal, temporal, parietal and occipital areas (4) prior to administering drugs to the 5 patients used in this direct addiction test. In 3 of these, the subsequent effect of a single 300-mg dose of carisoprodol was ascertained about one hour after carisoprodol was administered orally. In a similar manner, the effects of a single dose of 1,000 mg were determined in one patient, and those of 2,000 mg in another patient. During the direct addiction test, EEGs were taken on all 5 patients one hour after the 10 a.m. medication, when a daily dosage of 4,200 ot 4,800 mg had been attained. The patient receiving carisoprodol for 54 days had an additional EEG after 45 days on the drug. During withdrawal, each of the 5 patients that had taken carisoprodol for 18 days had an EEG 18 and 36 hours after the last dose, and the patient that had carisoprodol for 54 days had one EEG 13 hours and another at 24 hours after the last dose.

Results. — During chronic administration of carisoprodol, except for changes in the EEG pattern, the outstanding feature was a complete absence of any significant subjective effects even when the dosage was increased to 4,800 mg daily. In other words, it was not possible to differentiate carisoprodol from a placebo (figure 1).

Following abrupt withdrawal of carisoprodol, the 4 patients that received it for 18 days showed no autonomic signs of abstinence, and did not realize that their medication had been changed. TAS scores (total scores under the time-action curve during the 10 days of withdrawal) averaged 77.3 during withdrawal as compared with an average TAS score of 41.0 observed during their last 10 days on carisoprodol. This increase in the abstinence scores during withdrawal is insignificant, particularly in view of the fact that the maximum daily score was only 10.3 points during withdrawal. The patient who received carisoprodol for 54 days showed no signs of abstinence when the drug was discontinued abruptly; the TAS score was 38 points, and the maximum daily score was only 7 points. This patient likewise stated that at no time did he feel the medication, and he was completely unaware of the fact that carisoprodol had been discontinued.

The EEG pattern after single doses of 300 mg showed questionable barbiturate-like effects as compared with the pre-drug EEG, but after single doses of 1,000 and 2,000 mg, and during chronic intoxication (4,200-4,800 mg daily), barbiturate-like effects were obtained. These changes consisted of rhythmic and non-rhythmic low- and medium-voltage fast activity (18-32 cps) seen more prominently in the frontal leads. In the 4 men who received carisoprodol for 18 days, the EEG patterns 17 and 36 hours after the last dose of the drug were normal. In the case of the patient who took carisoprodol for 54 days, the first EEG, taken 14 hours after the last dose of carisoprodol, showed a barbiturate-like effect, but the one taken 36 hours after the last dose was normal. None of these patients showed focal or generalized abnormalities of the paroxysmal type during withdrawal, such as those seen following withdrawal of barbiturates (9, 13, 4).

None of the clinical observations or laboratory tests showed significant deviations from pre-drug observations.

Chronic administration of carisoprodol on a progressive dosage schedule did not induce a characteristic barbiturate intoxication pattern (nystagmus, dysarthria, ataxia in gait and station, confusion, poor judgement and loss of emotional control), and when carisoprodol was abruptly withdrawn, no signs of barbiturate-like abstinence (anxiety, fine tremor, weakness, convulsions and delirium) were observed (9). However, it remains to be seen whether administering carisoprodol continuously in larger doses would induce a chronic state of intoxication and whether abrupt withdrawal under such circumstances would provoke a barbiturate or meprobamate type of abstinence. Such a possibility is suggested

by the fact that carisoprodol is a congener of meprobamate and exhibits many barbiturate-like pharmacological effects.

Part II. — Phenyramidol

1. *Effects of Single Doses*

Methods. — These were the same as those described for carisoprodol.

Results. — Seventeen tests in a dose range of 100-750 mg were conducted using non-tolerant subjects; 6 patients received the maximum dose of 750 mg. No effects were reported after any of these doses by any patient or observer, except sleepiness, which was noticed by one patient after a 750-mg dose. The pupils were not constricted. Neither the patients nor observers identified phenyramidol as an opiate; in fact, the most impressive finding was an absence of detectable objective or subjective pharmacological effects in these tests.

2. *24-hour Substitution of Phenyramidol for Morphine*

Methods. — These were the same as those outlined for carisoprodol.

Results. — Phenyramidol in a total dosage of 1,500 mg (divided into three equal doses) was substituted for 240 mg of morphine sulfate in 9 patients, and was compared with morphine (continued in the customary dosage) and with a placebo substituted in other tests using the same patients. As compared with a placebo, phenyramidol slightly depressed symptoms of abstinence from morphine, but the degree of suppression was statistically insignificant (figure 2).

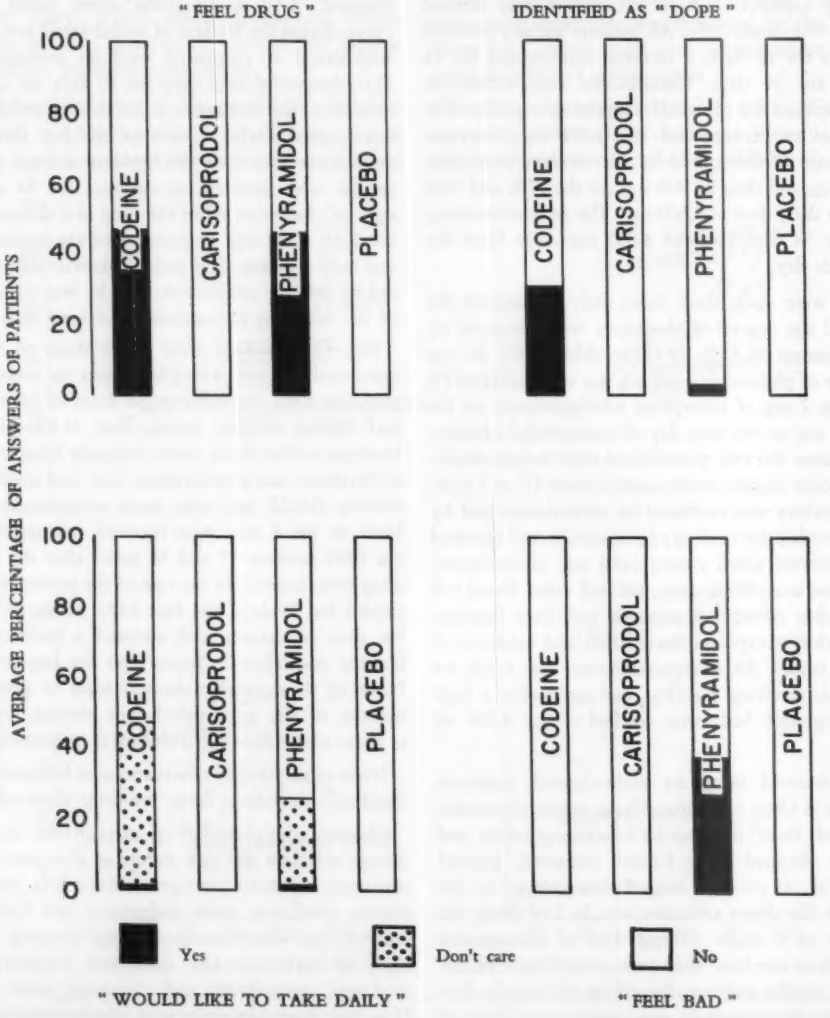

Figure 2. *Ratings of patients during direct addiction tests.* A comparison of the average percentage responses to the single dose questionnaire (patients' ratings) for codeine, carisoprodol, phenyramidol and a placebo for the parameters " feel drug ", " identification as ' dope ' ", " would like to take daily ", and " feel bad ". The comparison between codeine and a placebo was made with the same subjects in the same experiment, but other comparisons between drugs were made in analogous but different experiments using different subjects.

3. *Direct Addiction to Phenyramidol*

Methods. — Four non-tolerant subjects were used in a double-blind test — i.e., neither patients nor observers were aware of the nature and schedule of medication. Starch placebo and phenyramidol powder were prepared in identically appearing capsules, and all medication was divided into four equal doses daily. Initially all patients received placebo capsules for 7 to 10 days, then all were given phenyramidol for 18 days, after which the drug was abruptly withdrawn for two days. Medication was then resumed for an additional 42 days. The initial daily dose of phenyramidol was 600 mg, which was progressively increased until a daily dose of 4,500 mg was attained by the 18th day, and an attempt was made to stabilize patients on this dosage for the remainder of the experiment. After a total of 61 days of chronic drug administration, phenyramidol was withdrawn on a double-blind basis by replacing it with identically appearing placebo capsules.

Observations were the same as those made for evaluating carisoprodol, except EEGs and EKGs were not obtained.

Results. — One patient took phenyramidol for 16 days. The experiment was terminated on the 17th day, when a dosage of 4,200 mg had been attained, because he had diffuse urticaria. Prior to this, the only symptom noted by this patient was " sleepiness ". No symptoms or signs of abstinence developed after phenyramidol was discontinued, and the urticaria gradually subsided.

The other 3 patients attained a daily dose of 4,500 mg by the 18th day, and when medication was withdrawn abruptly for two days they showed no evidence of abstinence. Medication was resumed on the 21st day, but it was necessary to reduce the dosage of two patients to 3,300 mg daily because of such complaints as indigestion, sleepiness, dizziness and numbness of the skin (figure 2). One patient continued on 4,500 mg of phenyramidol daily, but he had a multiplicity of complaints; for example, he stated ". . . It made my face feel numb, I got a buzzing in both ears, and I had trouble hearing." He also described a sensation at times resembling effects of benzedrine or cocaine, which would last for only a few minutes. On the other hand, he had a relaxed feeling when he laid quietly in bed. Since these effects appeared contradictory to him, he inquired as to whether his medication had been changed from time to time. None of the patients liked the effects of phenyramidol, and the high incidence of " feel bad " reports as compared to the zero incidence of such reports during chronic intoxication with codeine is noteworthy (figure 2).

After 61 days of chronic intoxication, none of these patients realized that placebo capsules had been substituted. Abstinence scores were insignificant; in fact, they were smaller than comparably computed scores obtained while receiving phenyramidol.

Discussion

In the tests employed, neither carisoprodol nor phenyramidol showed any addictive properties of an opiate type. Although carisoprodol is pharmacologically similar in certain respects to barbiturates, it is not as rapidly acting as certain barbiturates. When the dosage of carisoprodol was rapidly increased from 1,200 to 4,800 mg daily within a period of 18 days, no evidence of intoxication was noted — suggesting that some tolerance developed to the sedative and hypnotic effects.

Summary and conclusions

The addictiveness of orally administered carisoprodol and phenyramidol has been studied in former opiate addicts. The procedures included effects of single doses, substitution tests to suppress abstinence from morphine, and direct addiction tests.

It is concluded that neither carisoprodol nor phenyramidol possesses addictive qualities of an opiate type.

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Drug control in Sweden

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For many years drugs to be introduced on the market in Sweden have been submitted to strict control measures. These apply to chemical compounds used as drugs as well as to biological products, to single substances as well as to mixtures or compositions, including narcotic and habit-forming drugs. The effect of the existing laws has been to facilitate the introduction of new products of value, to protect the public from using drugs of doubtful or no value, and to keep down the cost of medication.

The aim of this study is to give a survey of the existing lesgislation, its administration and general effects.

A. Main types of products on the Swedish market

1. *Place of Sale*

The major portion of the retail sale of medicines in Sweden is monopolized and is limited to the pharmacies, about 540 in all, corresponding to one pharmacy for 14,000 individuals.

For distribution of certain necessary medicines in less populated areas, about 800 distribution centres have been set up, connected to the pharmacies and keeping in stock a limited number of medicines not on prescription. The pharmacies, which are owned privately, co-operate very closely and have formed a financial and administrative union (Apotekarsocieteten) with strict and detailed rules for all the members of the organization, approved by the Ministry of the Interior.

The turnover of the pharmacies in 1960 was about 400 million crowns, two-thirds of this sum being for sales on prescription. Eighty-five per cent of the prescriptions comprised pharmaceutical specialities (proprietary products) and "standardized" galenic preparations (see below), the rest being *ex tempore* preparations.

Cosmetics, some common preparations for fresh wounds, hair lotions, certain saline laxatives, liniments and some vitamin preparations may also be sold outside the pharmacies. These products are controlled by a special council, supervising the advertising of these products. The National Board of Health appoints one of the members of this council. The other members are from the press, industry and the advertising field. The council operates mainly in an advisory capacity, but has the means to stop misleading advertising in the newspapers, magazines and other periodicals.

2. *Drugs on the Market*

The products sold by the pharmacies comprise pharmaceutical specialities (proprietary products) and other preparations, mostly galenicals.

(a) *Pharmaceutical Specialities (Proprietary Products)*

The greater part of the medicines sold in Swedish pharmacies are pharmaceutical specialities (proprietary brands). By these are meant preparations sold to the user in the container in which they are supplied by the manufacturer. The sale of these products is controlled by the royal ordinance concerning trade in pharmaceutical specialities of 15 June 1934 (Specialitetskungörelsen).

Prior to the introduction of this ordinance, the market was flooded with so-called patent medicines, many of extremely doubtful value. The introduction of the regulations in 1934 resulted in a much needed clean-up in this field.

The number of specialities on the Swedish market in recent years has been between 2,000 and 3,000, which is considerably less than in most other countries.

About half of the pharmaceutical specialities are of Swedish origin: the rest are imported. The number of remedies accepted for sale has varied somewhat from year to year, and shows a slight tendency to increase (fig. 1).

All addiction-producing drugs, covered by international treaties, are also controlled in Sweden. The number of addiction-producing drugs actually sold on the Swedish market and covered by international treaties is, however, considerably less (14 only), distributed among 62 proprietary products, containing one drug only or compositions.

The narcotics sold on the Swedish market include, besides opium, the following opium derivatives: morphine, codeine, ethylmorphine, hydrocodone, hydromorphone and oxicodone. Among synthetic drugs with morphine-like properties, 8 drugs are sold: dextromethadone, dextromoramide, diethylthiambutene, ketobemidone, methadone, normethadone and pethidine.

Some preparations containing codeine in combination with other active ingredients are exempt from prescription, while preparations containing ethylmorphine plus an active ingre-

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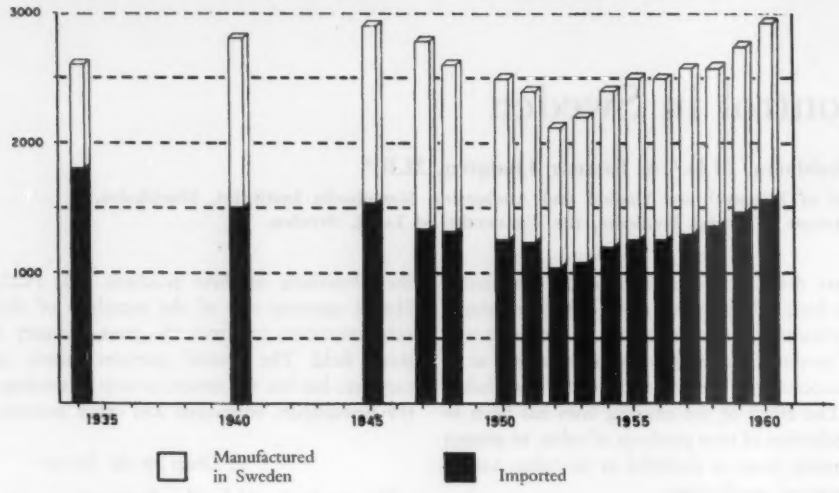

Figure 1

Number of pharmaceutical specialities, registered or sold on general ad interim *sales permit in Sweden, 1934-1960*

dient are exempt from narcotics control, but are on prescription.

Exempt from narcotics control are also dextromethorphan and pholcodine.

Cocaine is used as a local anaesthetic only in exceptional cases, and delivered as an *ex tempore* preparation.

Stimulating drugs on the Swedish market which are likely to be abused — e.g., agents used therapeutically for obesity, but abused to a growing extent especially by juveniles — and not covered by international treaties, can be designated as narcotics under existing Swedish laws. Seven stimulating drugs distributed among 20 proprietary products on the market have been declared narcotic drugs — viz., acetyloxiphenylmethyl piperidine, amphetamine, dexamphetamine, metamphetamine, methylphenidate, phenmetraline and pipradol.

The number of analgesic drugs not on prescription — mainly drugs with antipyretic properties — is about 60.

The number of substances on prescription with sedative, tranquillizing or ataractic properties is about 50, distributed among about 210 proprietary brands.

(b) *Other Preparations (including Galenics)*

Each pharmacy is equipped to produce a composition *ex tempore* according to an individual prescription. As a rule an *ex tempore* galenic preparation is prepared in the pharmacy to which the prescription is delivered. Within the pharmaceutical organization, however, there is considerable manufacture of those non-proprietary products which do not deteriorate easily, can be kept in stock indefinitely, and have a " standardized " composition. This manufacture is confined to 18 district laboratories connected with certain pharmacies and equipped for manufacture on an industrial scale.

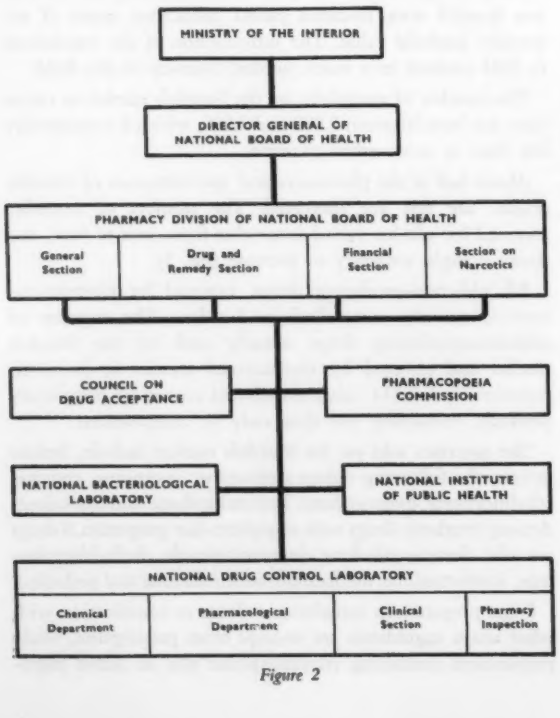

Figure 2

B. Organization of the National Drug Control Authorities

1. *The National Board of Health*

The National Board of Health (Kungl. Medicinalstyrelsen), headed by a director-general, is the executive and administrative organ of the Swedish Ministry of the Interior for questions regarding public health.

The board comprises a number of administrative units divided into sections. The unit managing drug control and the supervision of the pharmacies is the pharmacy division, divided into four sections (fig. 2).

The general section supervises the quality and the manufacture of medicines in the pharmacies and in the district laboratories.

The drug and remedy section has the responsibility for the introduction and control of proprietary products, and handles questions regarding the import, export and sale of pharmaceutical specialities.

The financial section supervises and confirms the prices of the raw products and medicines that are manufactured and sold by the pharmacies. It also investigates the prices of the industrially produced preparations.

The narcotic section handles questions regarding narcotic drugs — i.e., import, export, sale and legal matters concerning these drugs.

A close co-operation exists between the different sections. The pharmacy division works more as a team of different specialists than as a unit split up into separate sections, the head of the general section being a pharmaceutical chemist, and the head of the drug and remedy section a physician and an expert in pharmacology. Legal experts are attached to the different sections.

2. *The National Drug Control Laboratory*

The National Drug Control Laboratory (Statens farmaceutiska laboratorium) has as its main task the proper control of drugs to be introduced on the market or already on the market.

The laboratory is directly connected with the National Board of Health, and is divided into three departments and one section (fig. 2).

The chemical department carries out chemical and pharmaceutical control as well as research within these fields, and advises in matters concerning the classification of substances according to the statute on poisons, and other national and international requirements.

The pharmacological department covers biological assay of pharmaceutical products and carries out research on the action and uses of drugs, including specific work on biological standardization — e.g., the preparation of biological standards.

A special section attached to the pharmacological department deals with problems of clinical pharmacology and experimental therapeutics, with special regard to assessing the clinical value of drugs intended for sale on the market and evaluating indications, possible side actions and claims regarding use of products.

The pharmacy inspection supervises the production of galenic preparations in the pharmacies and collects samples of drugs in the market which are to be analysed in the laboratory for purposes of market control.

Close co-operation exists between the National Drug Control Laboratory and other governmental or semi-governmental agencies. Assay of antibiotics and control of sterility of solutions intended for injection are handled by the National Bacteriological Laboratory. Vitamin analyses of pharmaceutical specialities are carried out by the vitamin department of the National Institute of Public Health. The control laboratory of the Swedish Pharmaceutical Society (AKL) is responsible for most of the control of raw materials and other products distributed to and used in individual pharmacies. This laboratory also edits the list of standard preparations prepared in the pharmacies and proprietary products allowed to be sold in Sweden.

3. *The Council on Drug Acceptance*

The Council on Drug Acceptance (Specialitetsnämnden) advises the National Board of Health on the acceptance or refusal for sale of proprietary products.

The council consists of five voting members, all appointed by the Government. The chairman is an expert in jurisprudence, holding a prominent governmental position; the others are experts representing internal medicine, pharmacology, pharmacy and the chemical industry. The head of the drug and remedy section, as well as the representatives of the various departments of the National Drug Control Laboratory, participates in the discussions of the council, but has no right to vote.

In the case of new products to be introduced on the market, the council advises the National Board of Health whether the product shall be registered as a pharmaceutical speciality with the board and given a permanent sales permit, or whether other measures shall be taken. Other tasks of the council include consideration whether a product should be considered a pharmaceutical speciality or not, establishment of general principles regarding indications for use of special groups of substances, and special measures regarding advertising of narcotic products, etc. With regard to products already on the market and subject to control, the council can advise whether or not the product is to remain on the market.

The council may also be consulted in special cases concerning the classification of new products according to the statute on poisons or to national or international narcotics legislation.

C. Basic principles of drug control

The basic laws now in effect concerning the sale of drugs in Sweden are the royal statute on pharmaceutical products of 1913 (1), the royal statute of poisons of 1943 (2), the royal ordinance concerning the control of and trade in certain bacteriological preparations intended for human use of 1925 (4), and the royal ordinance concerning trade in pharmaceutical specialities of 1934 (5).

Regulations concerning addiction-producing drugs are to be found in the royal ordinance concerning narcotics of 1933 (3). Besides these regulations, Sweden is bound by existing international treaties concerning addiction-producing drugs.

All *ex tempore* preparations according to a doctor's, a dentist's or a veterinary's prescription must be made by a licensed pharmacist. The *ex tempore* preparations are not controlled *per se*. Instead, the pharmacy inspectors have to

check whether raw materials or other substances used for making the *ex tempore* preparations and stored in the pharmacies are in good condition and fulfil the requirements of the Swedish Pharmacopoeia. They also ensure that the arrangements for the preparation of the final products are satisfactory from the point of view of safety and the elimination of errors.

The production of galenic preparations by the district laboratories is controlled by the control laboratory of the Swedish Pharmaceutical Society (AKL). As a routine matter, samples are also taken in the market by the pharmacy inspectors and analysed at the National Drug Control Laboratory.

Due to the impossibility of controlling the industrial production of pharmaceutical products (proprietary brands) in the same manner as the pharmacy preparations — i.e., at the place of production — the control of the pharmaceutical specialities is based on the examination of the final product, before it is introduced on the market, and at regular intervals after its introduction (7).

The introduction of new drugs is subject to sales permits granted by the National Board of Health.

The sales permits are divided into three categories:

(1) The individual sales permit (licence), granted to a doctor, a veterinary surgeon or a dentist after special application;

(2) The general *ad interim* sales permit; and

(3) The permanent sales permit (registration).

The sales permits may if necessary be revoked by the National Board of Health.

As the sale of the pharmaceutical specialities is restricted to the pharmacies, which are under strict control by the government, the distribution of the proprietary products, their introduction and release as well as their prohibition for sale is effectively administered by the national drug control authorities.

D. Registration of pharmaceutical specialities

The principal prerequisite for the sale of a pharmaceutical speciality on the Swedish market is the inclusion of the product in the register of the National Board of Health. Hence, the manufacturer or his representative must apply to the National Board of Health for registration of the preparation in order to be allowed to sell the product, submitting relevant material, including samples of the product to be sold.

After the application has been filed at the National Board of Health, the first task is to decide if the product or the preparation is " intended to prevent, ameliorate or cure disease or symptoms of disease in man or animals ", and falls under the ordinance concerning trade in pharmaceutical specialities.

The royal ordinance concerning trade in pharmaceutical specialities (1934) (5) states that the National Board of Health, when a compound or a preparation is intended for sale, must pay special attention to five major points:

(*a*) Whether the statement of the character and composition of the speciality is correct;

(*b*) Whether the speciality is appropriate from a pharmaceutical point of view;

(*c*) Whether the speciality can prevent, ameliorate or cure disease or symptoms of disease in man or animals — i.e., is medically useful;

(*d*) Whether the price of the speciality is fair;

(*e*) Whether the claims made in the advertising material are justified.

After a first survey of all relevant data has been made by the Drug and Remedy Section of the Board, the material, including samples of the drug, is sent to the National Drug Control Laboratory, where the actual control is carried out.

The control measures at the National Drug Control Laboratory are intended to check the points as outlined above. In order to concentrate the studies on essential features, a procedure for each single drug to be controlled is drawn up at regular meetings between the head of the drug and remedy section of the National Board of Health and the staff of the National Drug Control Laboratory. The actual work carried out is intended to obtain information on five major points:

(a) *Composition*

A fundamental prerequisite for registration is a correct statement of the composition of the speciality. This applies to the principal active constituents as well as to any other substance present in the product. The individual constituents are tested qualitatively and quantitatively by chemical methods.

In those cases where chemical methods are not specific or sensitive enough, biological assay is carried out. The testing is made in comparison with reference standards, sent in by manufacturers in case of new substances or with the appropriate international biological standards when the drug is biologically assayed. Examples of products which are tested biologically at the laboratory are digitalis preparations and hormones.

Preparations including antibiotics are tested in the National Bacteriological Laboratory. The same applies to sterility tests of compounds intended for injection.

Preparations containing vitamins are tested in the vitamin department of the National Institute of Public Health.

A further measure in the control of the composition of a speciality is the requirement that the actual declaration of the contents of the drug be written in a standardized form, according to the Swedish Pharmacopoeia or national or international specifications. This implies, amongst other things, the use of generic names instead of proprietary names or codified chemical names for substances not yet assigned an international non-proprietary name.

A moderate variation of the declared content is usually allowed. In the case of a significant departure from the declared content, the manufacturer may be told of the results, and an explanation is sought before a final decision is reached. This means that several causes are investigated as a possible reason for the difference — e.g., deterioration of the product with time or various methods of assay.

Usual causes for rejection of the registration are departures from the declared content not satisfactorily explained or the finding of substances or other products not accounted for in the declaration.

(b) *Pharmaceutical Suitability*

The quality of the product is thoroughly tested from a pharmaceutical point of view, as a rule according to the standards and the criteria of the Swedish Pharmacopoeia. The product's rate of deterioration is considered as specially important, and in many cases special tests are made to check this rate.

Important causes for rejection on grounds of pharmaceutical suitability are a high rate of deterioration or a large variation in the final product.

(c) *Medical or Therapeutic Usefulness*

The experimental data on the action of the product or its active constituents in animals and man are thoroughly evaluated. Claims to an activity greater than that of other products are judged on the basis of comparative experiments.

Data supplied on acute toxicity (LD_{50}) as well as chronic toxicity tests in the case of products intended for prolonged use are considered, and toxicity data in various species and on similar substances are compared.

The medical and therapeutical usefulness is evaluated primarily by studying the available literature on the preparation as well as the results of experimental and clinical tests not yet published.

The clinical data are evaluated and stress is laid upon those clinical trials that are designed to prove the "pure" or "net" action of the product as differentiated from other effects (hospitalization, psychological measures) or other treatment given concomitantly.

If a product has been used for a number of years in other countries and a comprehensive and adequate body of experiments and clinical experience is available, a review of the pertinent literature is usually sufficient for assessing the medical usefulness of a drug.

If the documentation is considered insufficient, however, as a first step the manufacturer or his representative is requested to present further support for the stated indications before a decision is reached. Sometimes a manufacturer is advised to arrange a controlled, statistically designed, clinical trial with the purpose of assessing the value of the product. Such a trial should if possible be organized as a double-blind study using control and test subjects with placebo administration. In the case of new products intended for use in a disease where specific treatment is already available, a double-blind study is suggested, using the best existing available specific treatment in the control group and the new drug to be studied in the test group.

Stress is also placed on the kind and frequency of side-actions and possible toxic reactions. Among these may be mentioned allergic symptoms, undue toxicity with regard to liver and kidney functions, the appearance of harmful disturbances in the hemopoietic system — e.g., methemoglobinemia or agranulocytosis — or toxic reactions from other organs — e.g., from the gastro-intestinal tract (hyperacidity, bleeding). Effects on the central nervous system — e.g., fatigue, drowsiness or sleepiness in the case of antiallergical preparations intended for day-use — or other symptoms are also considered.

Consideration is given not only to clinical manifestations of the drug in question, but also to known toxic actions of similar substances with parent chemical structure — e.g., possible liver toxicity by phenothiazine derivatives or bone marrow damage by amidopyrine compounds.

With regard to new substances with strong analgesic or antitussive action, special attention is paid to the possible addiction liability of such substances. Special attention is also paid to substances with stimulating properties and likely to be abused. Sweden complies with the international treaties in this respect, but may also declare substances which are abused to a high extent, but are not included among those internationally declared as addiction-producing drugs, as narcotic drugs and submit them to the same measures as are laid down for narcotics. This is the case with, for example, acetyloxiphenyl-methyl piperidine, amphetamine, dexamphetamine, metamphetamine, methylphenidate, phenmetraline and pipradol. These drugs are mainly used therapeutically for obesity or in certain nervous or mental states, but are beginning to be abused to a growing extent by juveniles and narcotic addicts.

The final step in the evaluation of the medical and therapeutic usefulness is to consider the indications and contra-indications actually claimed for the clinical use of the product intended for sale.

The usual causes of rejection of a preparation for therapeutic reasons are unjustified claims as to the clinical effect which the manufacturer is unwilling to withdraw, or a high incidence of untoward side-actions.

(d) *Price*

Questions regarding price are handled by the financial section of the pharmacy division of the National Board of Health working in close co-operation. The price of the product is examined on the basis of the cost of the raw products, primarily taking into consideration the reasonable cost of production of the new compound. Other grounds for consideration are a comparison with the price of similar products which can be made as *ex tempore* preparations or which already exist as standardized preparations.

(e) *Advertising*

The advertising material appended to the application for registration is examined with regard to the statements concerning indications, contra-indications and possible side-actions. Claims as to a favourable clinical effect, based upon reports comprising a few cases only and without controls, are considered as not justified, and have to be withdrawn if the product is to be sold.

When the investigation has been completed at the National Drug Control Laboratory, the bacteriological laboratory and the vitamin laboratory, and the price of the product has been established by the financial section of the pharmacy division, the results are presented to the Council on Drug Acceptance.

The Council on Drug Acceptance makes its recommendations based on the information gathered by the control agencies mentioned, and on experience and studies available from other sources.

The Council first decides on the basic question of whether the application for a permanent sales permit (registration) of a new product shall be granted or not. If the council recommends that registration be granted, the National Board of Health has the choice of following the recommendation or not. If the council recommends the rejection of an application, the National Board of Health is bound to concur.

If the information available is scanty or it is considered too early to assess the final value of a product, the council may defer its decision and may propose that the drug be sold on an individual sales permit or on a general *ad interim* sales permit (see section E), until more information on the use of the drug has been collected by doctors, hospitals, etc. In doubtful cases the council may propose further steps to be taken by various agencies before a final recommendation is made. In some cases the council may suggest specific studies to be carried out, recommending that the manufacturer or his representative induce interested hospitals or research workers to carry out a controlled clinical trial, based on a statistically designed plan with adequate controls.

In questions of major and fundamental interest the council may suggest an impartial study, designed as a statistically controlled clinical trial to be carried out by a special therapeutic trials committee appointed by the National Board of Health.

As examples of such investigations, mention might be made of three series of studies on the efficacy of chemotherapy in pulmonary tuberculosis, assessing the value of para-aminosalicylic acid (PAS), streptomycin and isonicotinohydrazide (INH). The first study in this series, carried out in 1948, consisted of a comparison between the effect of PAS in the test group and hospital treatment plus a placebo in the control group, because at that time no specific treatment was available. During the next study, carried out in 1950, placebo treatment could not be instituted, and the effect of PAS in the test group was compared to that of streptomycin in the control group. The third study in 1952 on the efficacy of INH was organized first as a comparison between INH in the test group and streptomycin in the control group, and later as a comparison between INH plus PAS in the test group and streptomycin plus PAS in the control group.

Other studies of this kind carried out by the therapeutic trials committee comprise an investigation of the use of antihistamines in the common cold (13), and a study on the efficacy and possible side-actions of phenylbutazone in rheumatoid arthritis (14, 15, 16).

The final decision on the acceptance or the rejection of a new drug for sale is made by the National Board of Health, based on the advice given by the Council on Drug Acceptance. When the Board of Health accepts the drug it is included in the register of pharmaceutical specialities and given a registration number. This means a permanent sales permit as specified in the royal ordinance concerning trade in pharmaceutical specialities (1934).

If the application is rejected, the rejection is published and included in a separate list comprising the pharmaceutical specialities that are not to be sold.

E. Ad interim sales permits

The investigation of new drugs by the control authorities is very thorough and may require a long time. Procedures have therefore been introduced to make it possible to introduce pharmaceutical specialities on the market before the product is finally registered. Two such *ad interim* sales permits exist, an individual, temporary *ad interim* sales permit, and a general *ad interim* sales permit.

1. *The Individual Temporary* ad interim *Sales Permit (licence)*

Individual *ad interim* sales permits (licences) are issued by the National Board of Health. As a rule, a licence is granted without any delay if a doctor, a veterinary surgeon or a dentist certifies that the preparation is to be used for scientific purposes only, or for a particular patient who can be shown to be in need of the preparation for the treatment of a specified disease.

The licence applies to a particular pharmacy and for a definite quantity of a certain drug. The drug will be delivered only on a prescription from the doctor, veterinary surgeon or dentist who has certified its need.

The individual *ad interim* sales permits are issued primarily for four different kinds of drug:

(*a*) Drugs no longer imported or produced, which the manufacturer has been permitted to withdraw from registration;

(*b*) Proprietary products which have not been filed for registration;

(*c*) New drugs recently filed for registration but not yet registered and not given a general *ad interim* sales permit; and

(*d*) Certain biologically active new drugs, where the clinical experience is not yet adequate to judge whether the drug has real value or not, or where it has not been possible to assess the real frequency of possible side-actions.

The licence procedure permits the board to obtain more detailed information about the drug than if the drug were to be sold freely. This information may come from the doctors that are using a new drug, and concerns the kind of disease treated, the indications and contra-indications for use and the number of patients actually obtaining the drug. Licensing was used for this purpose to a great extent during the years 1944 to 1948, when there was a limited supply of antibiotics and the use had to be restricted to patients really in need of these drugs — mainly penicillin and streptomycin.

The licence procedure can also be applied with regard to new analgesics or antitussives, the possible addiction liability of which has not been ascertained, and with regard to stimulating substances or other agents — e.g., those used for weight-reducing purposes — which are likely to be abused. This means that the number of doctors prescribing a certain drug, the number of patients getting it and the indications on which the drug is given can be controlled efficiently. If the drug were immediately released for sale, control measures would have to come afterwards — and in some cases too late.

Keeping a drug on licence while registration is pending has still another advantage. It makes it easier to induce the manufacturer to withdraw unjustified claims than if the preparation were already registered, because no licence will be issued until the manufacturer has complied with the existing rules.

The number of individual licences applied for in 1958 was 8,214, and in 1959, 9,798. The licences concerned about 800 different drugs; of these, 400 concerned drugs not yet being filed for registration, about 200 concerned drugs where registration was revoked (see section F) and 200 concerned drugs where application for registration was pending.

2. *The General* ad interim *Sales Permit*

The usual action while a preparation is under consideration for registration is to issue a general *ad interim* sales permit for the product as early as possible. The permit is given, if no severe objections have been raised against the introduction of the drug on the market, at a preliminary consideration in the National Board of Health, in the National Drug Control Laboratory and in the financial section of the pharmacy division.

The general sales permit denotes that the sale of the preparation is not restricted to a particular doctor or pharmacy or patient, as is the case with the individual *ad interim* sales permit. All those drugs, for which a general *ad interim* sales permit has been granted, may be sold in every pharmacy according to the general regulations for the selling of drugs, may be advertised in medical journals and they may be handled in several other respects as if they already had been registered.

The general *ad interim* sales permit is issued by the National Board of Health by entering the preparation on the so-called licence-free list (licensfria listan) and including the name of the preparation in the quarterly list of pharmaceutical specialities accepted for sale without special licence (Apotekens förteckning över standardförpackade läkemedel) (8). The product, however, is not given any registration number at this stage.

As a rule, in order to speed up proceedings and when the preliminary investigations of a drug disclose no grounds for serious criticism, the Council on Drug Acceptance is not consulted before a drug is placed on the licence-free list. Only in cases of doubt with regard to high frequency of side-actions, liability to produce addiction or abuse, or other specific grounds, are questions on the issuing of a general *ad interim* sales permit or individual temporary sales permits (licences) considered by the council.

The general *ad interim* sales permit as a rule remains in effect until the preparation is registered.

The drug may, however, be withdrawn from the licence-free list with immediate effect at any time by the National Board of Health. This implies that the general *ad interim* permit may be cancelled at any time and without the board having to consult the Council on Drug Acceptance. Such action may be necessary if, for example, during the further examination of the drug, factors should be found that necessitate immediate stopping of sale — e.g., undue toxicity, deviations from the declared content, unjustified claims in the advertising material, or too high a price.

The procedure of placing a preparation on the list of general *ad interim* sales permits (licensfria listan) has a high flexibility, and has proved very advantageous. Discriminate use of the licence-free list permits a good product which will be ultimately accepted to be sold shortly after the application for registration is filed, whereas a product not found fit for medical use can be rapidly withdrawn from the market.

On 1 January 1960 there were 2,488 registered specialities in Sweden and 353 drugs on the free list. The total number of drugs under application for registration at that time was 626. Thus, 57% of all new drugs were easily available on the market before the actual registration, the rest being available on licence only.

The final decision as regards registration may be delayed if it is considered advisable to obtain more data, especially regarding the clinical usefulness and the frequency of side-actions, before a product is definitely accepted. In this case the product is kept on licence or on the licence-free list, until a final decision can be made.

F. Market control and re-examination of registration

In accordance with the royal ordinance concerning trade in pharmaceutical specialities (1934), the National Board of Health, through its pharmacy inspectors, collects samples of the registered drugs on the market in order to ascertain whether they conform with the conditions under which they were accepted. Such market control is carried out routinely and usually with whole groups of products — e.g., hormones of various kinds, analgesics, chemotherapeutic agents, cardiac drugs, etc.

The control procedure may be instituted at any time for a certain drug if circumstances not apparent at the time of acceptance arise. Conditions which necessitate a market control may be an unexpected rapid deterioration of a preparation, an exaggerated or incorrect advertising campaign concerning the therapeutic value of the product or other laudatory remarks that might deceive the public, a sudden appearance of side effects from one or several batches of a product, a change in the composition of the product, etc.

The market control involves a partial or complete re-examination of the drug at the National Drug Control Laboratory,

including chemical, pharmaceutical and pharmacological rechecks and reassessment of the actual clinical value of the product in the light of the progress medicine may have achieved during the years which have elapsed since the introduction of the drug. The price is also reconsidered by the financial section.

If the re-examination during the market control shows that the registered product deviates from the original claims, the sale of the drug may be stopped by the National Board of Health by revocation of the registration. This means that the drug is cancelled from the specialities register — in urgent cases, immediately. Most commonly, however, the difference is reported to the manufacturer or his representative, and the manufacturer is given the chance of correcting the errors by his own efforts. If these fail or are considered inefficient, the question is referred to the Council on Drug Acceptance for consideration. After that, the registration may be cancelled by the National Board of Health.

The main difference between the revoking of the registration and the withdrawal of the drug from the licence-free list is that the control authorities can withdraw the drug from the licence-free list by immediate action, whereas the procedure for revoking the registration of a drug takes a certain time. This is one of the reasons that biologically active drugs may be kept on the licence-free list for a long time, as narcotics or drugs liable to be abused, if the clinical experience is insufficient for a final decision, or the frequency or severity of side-actions makes it likely that the clinical use of the drug may ultimately be restricted or not be allowed.

G. Prescription and classification according to the royal statute on poisons

In conjunction with the examination of a new product by the National Drug Control Laboratory, the question also arises of whether the product shall be sold over the counter or on prescription only. The decision is based mainly on the toxicity of the product, the indications and contra-indications for its clinical use, the frequency and kind of possible side-effects after therapeutic doses and after an overdose. The final decision is made by the National Board of Health.

The same procedure applies to the classification of a substance according to the royal statute on poisons.

Prescriptions for addiction-producing drugs under narcotic control cannot be re-used, and are filed at the pharmacies. This applies also to prescriptions for those drugs liable to be abused, which are placed under narcotic control by the Ministry of the Interior — viz., acetyloxiphenylmethyl piperidine, amphetamine, dexamphetamine, metamphetamine, methylphenidate, phenmetraline, pipradol. The authenticity of the narcotic prescription may be checked by the pharmacist by telephoning back to the doctor.

H. Narcotics control measures

The narcotics prescriptions are collected, and can be subjected to control measures by the National Board of Health. Thus, it is possible for the board to check the number of prescriptions issued by a certain doctor, the drugs prescribed, the amount, and the names of the patients. Further, it is possible to check the prescription of a certain patient, how often the patient has seen a doctor, the number of prescriptions obtained, the kind of drugs, etc.

With regard to the medical profession, several lines are followed. Doctors are informed of new developments. Advertisements of narcotic drugs or drugs liable to be abused must contain a warning concerning the risks of narcotic addiction or drug abuse.

As regards individual doctors, several steps can be taken. The first measure by the National Board of Health is to issue a warning to a doctor who has not been cautious enough in prescribing narcotics. The next step is a partial restriction of the prescription rights; only one or two pharmacies in the vicinity of the doctor will be allowed to accept his prescription. The third step is a complete abolition of the right to prescribe narcotic drugs for either a short or long period. The final step is a revocation of the licence to practice medicine.

Close co-operation exists between the National Board of Health, the pharmacies and the police authorities. Criminal cases may include doctors prescribing more narcotics than is advisable from a medical point of view for themselves or for patients, or other individuals suspected of abusing narcotics by obtaining prescriptions for narcotic drugs from a number of doctors, or being involved in illegal drug traffic (17).

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Microchemical identification of modern analgesic drugs (part II)

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Introduction

Since the publication of a previous paper on the identification of analgesic drugs (Clarke, 1959 a), additional substances have been brought under international control, or recommended for such restriction. It is the purpose of this paper to describe tests for seventeen of these new compounds.

It must be realized that the ever-increasing number of alkaloidal substances available makes their identification progressively more difficult. Although crystal tests are excellent for final confirmation when the compound has already been tentatively identified, they do not lend themselves to the " pinpointing " of one unknown substance out of the hundreds now in use for one purpose or another. Colour tests are more useful for this purpose, but are in many cases not available. To overcome this difficulty use may be made of paper chromatography, the system used by the writer being that described by Curry & Powell (1954). It is not proposed to consider here the details of paper chromatography, for which the reader is referred to the excellent paper by Genest & Farmilo (1959); but it must be emphasized that Rf values are not strictly reproducible, and no attempt should be made to effect an identification on the Rf value alone. Paper chromatography does, however, serve a most useful purpose in narrowing the field for identification by crystal and colour tests. Should it be necessary, these tests may be carried out on material eluted from the paper chromatogram (Clarke, 1960 a; Clarke & Hawkins, 1960).

Results

Table 1 gives the approved name for the compound, its chemical name and the Rf value on the Curry & Powell system. Table 2 shows the type of precipitate obtained when a micro-drop of a 1% solution of the compound is added to a similar drop of the reagent. Table 3 shows the type of crystal obtained, those most suitable for identification purposes being printed in capitals. Table 4 shows the results of various colour tests. The composition of the reagents and the technique for carrying out the tests are as described previously (Clarke & Williams, 1955; Clarke, 1959 a).

Phenazocine and dimenoxadol have been included in the tables, although tests for these substances have already been described (Clarke, 1959 b; Clarke, 1960 b). R.951 (1-(3-oxo-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester) has also been included, because it appears to have outstanding analgesic properties (Janssen, Jageneau, Van Proosdij-Hartzema & de Jongh, 1958). This compound is the ketone corresponding to the secondary alcohol phenoperidine.

Discussion

It will be noted that while this group of new analgesic drugs includes derivatives of morphine, morphinan and pethidine, it also shows the introduction of fresh types of compound.

Some of these substances are not easy to identify; for example, hydromorphinol gives colour reactions similar to those of morphine, but even from concentrated solution forms few precipitates, only one of which is crystalline. Diampromide and phenampromide give no satisfactory colour reactions and few crystals. Levophenacylmorphan gives colour reactions that are not particularly characteristic; while the test with picrolonic acid is of little value, as the crystals form only from dilute solutions, and often fail to appear. Furethidine forms no crystals and gives only a single non-specific colour reaction. This substance is noteworthy on account of the number of precipitates which form as oily droplets.

Acknowledgements

My thanks are due to Dr. Nathan B. Eddy; Dr Harris Isbell; Dr. Paul Janssen; Dr. E. L. May; British Drug Houses Ltd.; Ciba (Basle) Ltd.; J. F. Macfarlan & Co. Ltd. and G. D. Searle & Co. Ltd. for supplying me with compounds used for this work. I am also greatly indebted to Miss Ann Cooper and Miss Sandra Gavin for technical assistance.

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TABLE 1. — SUBSTANCES TESTED

Approved name or INN	Chemical designation	Rf value
Allylprodine	3-allyl-1-methyl-4-phenyl-4-propionoxypiperidine	0.69
Benzethidine	1-(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	0.82
Clonitazene	2-(*para*-chlorbenzyl)-1-diethylaminoethyl-5-nitrobenzimidazole	0.66
Diampromide	N-[2-(N-methylphenethylamino) propyl] propionanilide	0.76
Dimenoxadol	2-dimethylaminoethyl-1-ethoxy-1,1-diphenylacetate	0.60
Diphenoxylate	1-(3-cyano-3, 3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	0.90
Etonitazene	1-diethylaminoethyl-2-*para*-ethoxybenzyl-5-nitrobenzimidazole	0.70
Furethidine	1-(2-tetrahydrofurfuryloxyethyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	0.64
Hydromorphinol	14-hydroxydihydromorphine	0.11
Levophenacylmorphan	(—)-3-hydroxy-N-phenacylmorphinan	0.77
Metazocine	2'hydroxy-2,5,9-trimethyl-6,7-benzomorphan	0.48
Norlevorphanol	(—)-3-hydroxymorphinan	0.58
Phenampromide	N-(1-methyl-2-piperidinoethyl) propionanilide	0.68
Phenazocine	(±)2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan	0.80
l-Phenazocine	(—)2h'ydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan	0.80
Phenoperidine	1-(3-hydroxy-3-phenylpropyl)-4-phenylpiperidine-4-carboxylic acid ethyl ester	0.84
Piminodine	4-phenyl-1-(3-phenylaminopropyl)-piperidine-4-carboxylic acid ethyl ester	0.72
R.951	1-(3-oxo-3-phenylpropyl)-4-phenyl-piperidine-4-carboxylic acid ethyl ester	0.86

TABLE 2. — TYPE OF PRECIPITATE OBTAINED

x = crystals a = amorphous o = oil o/a = oily amorphous - = no precipitate

Alkaloid ↓ / Reagent →	1 Gold bromide	2 Gold bromide/hydrochloric acid	3 Gold chloride	4 Lead iodide	5 Mercuric chloride	6 Picric acid	7 Platinum chloride	8 Platinum iodide	9 Potassium bismuth iodide	10 Potassium cadmium iodide	11 Potassium chromate	12 Potassium iodide	13 Potassium mercury iodide	14 Potassium permanganate	15 Potassium tri-iodide 1	16 Potassium tri-iodide 2	17 Potassium tri-iodide 3	18 Sodium carbonate	19 Sodium phosphate	20 Zinc chloride	21 Trinitrobenzoic acid	22 Platinum bromide	23 Picrolonic acid	24 Styphnic acid	25 Di-sodium methyl arsonate	26 Potassium cyanide	27 Ammonium thiocyanate
Allylprodine	a	o/a	o	x	o	x	x	a	a	o	o	–	a	a	o	–	o	–	–	–	x	a	x	x	–	o	o
Benzethidine	o	o	x	a	o	o	a	o	o/a	o	o	x	o	x	o	–	o	–	–	o	o	a	x	x	–	o	–
Clonitazene	o/a	x	o/a	a	x	a	a	a	a	a	x	x	a	a	x	x	o(x)	o	–	x	a	a	x	a	–	o	x
Diampromide	o/a	o	o/a	x	o	o	a	o	o	a	–	–	a	a	o	–	o	o	–	–	a	a	o/a	a	–	–	o
Dimenoxadol	a	a	x	x	x	o	x	o	a	a	a	–	o	o/a	o	–	o	–	–	–	x	x	x	x	–	–	–
Diphenoxylate	a	a	a	a	a	a	a	a	a	a	a	x	a	a	x	x	a	o	o	a	a	a	o/a	a	o	o	x
Etonitazene	o/a	x	a	a	o	x	a	a	a	x	x	x	a	a	x	x	x	a	–	o	a	a	x	a	–	–	x
Furethidine	o	o	o	o	o	o	o	o	o	o	o	–	o	o/a	o	–	o	o	–	–	o	o	o	o	–	–	o
Hydromorphinol	a	x	a	–	–	o	–	a	a	o	–	–	o	a	o	–	–	–	–	–	–	–	–	–	–	–	–
Levophenacylmorphan	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	–	a	a	–	a	a	a	a(x)	a	–	–	a
Metazocine	o	o	o	a	–	o	x	a	a	o	o	–	o	a	o	–	o	x	–	–	x	x	x	a	x	x	–
Norlevorphanol	x	x	x	a	x	x	x	a	a	o	a	–	o	a	o	–	o	–	–	–	o	x	o	a	–	–	–
Phenampromide	x	x	o	a	o	o	–	o	a	o/a	–	–	a	o	o	–	o	–	–	–	o	a	–	o	–	–	–
dl-Phenazocine	a	a	a	a	o/a	a	a	o	o	a	a	x	a	a	o	x	o	x	x	a	a	a	a	a	x	x	a
l-Phenazocine	a	a	a	a	a	a	a	a	a	a	a	o/a	a	a	o	–	o/a	x	a	a	a	a	x	x	x	x	o/a
Phenoperidine	o/a	o/a	o	a	o	o	x	o	o	a	x	x	a	x	o	x	o	o	–	–	o	x	a	o/a	–	–	o
Piminodine	a	a	a	x	o/a	x	x	a	a	o/a	x	x	o/a	a	x	x	x	o(x)	–	o(x)	x	x	a	x	–	–	x
R.951	x	x	x	x	o	o/a	x	o	o	a	x	x	x	x	x	x	x	o	–	o	a	a	a	a	o	o	x

TABLE 3. — TYPES OF CRYSTAL OBTAINED

o/n (overnight) = Crystals do not form until the following day.

Alkaloid and reagent	Type of crystal	Sensitivity (μg)
Allylprodine		
Lead iodide	Dense rosettes	0.1
Platinum chloride	Dense rosettes o/n	1.0
Picric acid	SMALL PLATES	0.25
Trinitrobenzoic acid	Dense rosettes	1.0
Picrolonic acid	Rosettes of rods	0.1
Styphnic acid	SMALL IRREGULAR PLATES	0.25
Benzethidine		
Gold chloride	SMALL PLATES o/n	0.1
Potassium iodide	Branching needles	1.0
Potassium permanganate	FEATHERY ROSETTES o/n	0.1
Picrolonic acid	Smudge rosettes o/n	1.0
Styphnic acid	Masses of blades o/n	0.25
Clonitazene		
Gold bromide/hydrochloric acid	Rosettes of curved needles	0.25
Mercuric chloride	Rosettes of rods	1.0
Potassium chromate	Bunches of blades	0.25
Potassium iodide	Bunches of plates	0.5
Potassium tri-iodide (1)	SMALL PLATES OR NEEDLES o/n	0.25
Potassium tri-iodide (2)	Bunches of plates o/n	0.25
Zinc chloride	VERY SMALL ROSETTES	0.1
Picrolonic acid	Small rosettes o/n	0.25
Ammonium thiocyanate	Bunches of plates	0.25
Diampromide		
Lead iodide	Dense rosettes and tablets o/n	1.0
Dimenoxadol		
Gold chloride	Bunches of needles o/n	1.0
Lead iodide	Rectangular plates	0.25
Platinum chloride	Small dense rosettes	0.25
Trinitrobenzoic acid	Small rosettes	1.0
Platinum bromide	ROSETTES OF BRANCHING RODS	0.25
Picrolonic acid	Small rosettes of rods	0.25
Styphnic acid	BUNCHES OF IRREGULAR PLATES	0.25
Mercuric chloride	Rhomboids	1.0
Diphenoxylate		
Potassium iodide	SMUDGE ROSETTES	0.25
Potassium tri-iodide (1)	Bunches of needles o/n	1.0
Potassium tri-iodide (2)	BUNCHES OF PLATES	0.25
Ammonium thiocyanate	Branching needles o/n	0.5
Etonitazene		
Gold bromide/hydrochloric acid	Curved oily needles o/n	0.25
Picric acid	Needles	1.0
Potassium cadmium iodide	Rosettes or feathery crystals	0.25
Potassium chromate	BUNCHES OF RECTANGULAR PLATES	0.25
Potassium iodide	Needles or blades	1.0
Potassium tri-iodide (1)	Dense rosettes o/n	1.0
Potassium tri-iodide (2)	Bunches of plates or prisms	1.0
Potassium tri-iodide (3)	Prisms or rosettes	1.0
Picrolonic acid	Bunches of prisms	0.25
Ammonium thiocyanate	BUNCHES OF RODS OR PRISMS	0.25
Furethidine		
—	—	—
Hydromorphinol		
Gold bromide/hydrochloric acid	VERY SMALL PLATES	1.0
Levophenacylmorphan		
Picrolonic acid	Small oily needles	0.25[a]
Metazocine		
Platinum chloride	Bunches of small plates	0.25
Sodium carbonate	DENSE ROSETTES OR PRISMS	0.25
Trinitrobenzoic acid	Segmented plates	1.0
Platinum bromide	Dense rosettes	1.0
Picrolonic acid	CURVING NEEDLES	0.25
Di-sodium methyl arsonate	Dense rosettes	1.0
Potassium cyanide	Dense rosettes	1.0
Norlevorphanol		
Gold bromide	Rosettes of needles	0.25
Gold bromide/hydrochloric acid	ROSETTES OF RODS	0.1
Gold chloride	Rosettes of rods	1.0
Mercuric chloride	Dense rosettes o/n	1.0
Picric acid	Dense rosettes o/n	1.0
Platinum chloride	IRREGULAR BLADES	0.5
Platinum bromide	Rectangular plates	0.5
Phenampromide		
Gold bromide	SERRATED BLADES	0.25
Gold bromide/hydrochloric acid	PLATES OR PRISMS o/n	0.25
dl-Phenazocine		
Potassium iodide	ROSETTES OF OILY NEEDLES	1.0
Potassium tri-iodide (2)	ROSETTES OF CURVING NEEDLES	1.0
Sodium carbonate	Bunches of prisms	1.0
Sodium phosphate	Rosettes o/n	1.0
Di-sodium methyl arsonate	Bunches of prisms	1.0
Potassium cyanide	Bunches of prisms	1.0
l-Phenazocine		
Sodium carbonate	FANS OF OILY NEEDLES o/n	1.0
Picrolonic acid	SHELL-LIKE CRYSTALS	1.0
Styphnic acid	Shell-like crystals	1.0
Di-sodium methyl arsonate	Fans of oily needles o/n	1.0
Potassium cyanide	Smudge rosettes o/n	1.0
Phenoperidine		
Platinum chloride	Dense rosettes o/n	0.25
Potassium chromate	Rosettes of rods	0.25
Potassium iodide	ROSETTES OF RODS	0.5
Potassium permanganate	PLATES OR BLADES	0.1
Potassium tri-iodide (2)	Dense rosettes o/n	1.0
Platinum bromide	Gelatinous or smudge rosettes o/n	0.25
Piminodine		
Lead iodide	Masses of needles	0.5
Picric acid	Curved branching needles	0.1
Platinum chloride	Sheaves of oily needles	1.0
Potassium chromate	BUNCHES OF BLADES	0.25
Potassium iodide	SMALL ROSETTES OF BLADES	0.25
Potassium tri-iodide (1)	Small irregular rosettes	1.0
Potassium tri-iodide (2)	Small irregular crystals	0.25
Potassium tri-iodide (3)	Small irregular crystals	1.0

TABLE 3. — TYPES OF CRYSTALS OBTAINED (contd.)

Alkaloid and reagent	Type of crystal	Sensitivity (γ)	Alkaloid and reagent	Type of crystal	Sensitivity (μg)
Piminodine (contd.)			Lead iodide	Oily blades o/n	0.25
Platinum bromide	Masses of oily needles o/n	0.25	Platinum chloride	Curved needles	1.0
Styphnic acid	Branching needles o/n	1.0	Potassium chromate	Rosettes of needles	0.1
Ammonium thiocyanate	Large needles o/n	1.0	Potassium iodide	Very small needles	0.25
Trinitrobenzoic acid	Dense rosettes o/n	1.0	Potassium mercury iodide	Curved needles o/n	1.0
			Potassium permanganate	Small plates or needles	0.25
R. 951			Potassium tri-iodide (1)	Rosettes of needles	1.0
Gold bromide	Oily needles	1.0	Potassium tri-iodide (2)	ROSETTES OF NEEDLES	0.25
Gold bromide/hydrochloric acid	Oily needles o/n	1.0	Potassium tri-iodide (3)	Bunches of oily needles	1.0
Gold chloride	Oily blades o/n	0.25	Ammonium thiocyanate	BUNCHES OF PLATES OR NEEDLES	0.1

[a] Crystals form from dilute solutions only.

TABLE 4. — COLOUR TESTS

Alkaloid	Marquis	Sensitivity (μg)	Ammonium vanadate	Sensitivity (μg)	Ammonium molybdate	Sensitivity (μg)
Allylprodine	Blue-black	0.1	Grey-green	1.0	Grey → green	1.0
Benzethidine	Orange	1.0	Orange-brown	1.0	Orange-brown	1.0
Clonitazene	—	—	—	—	Grey-blue	1.0
Diampromide	Orange	1.0	—	—	—	—
Dimenoxadol	Orange → greenish blue	0.1	Orange → brown → purple	0.1	Orange → brown → dull purple	0.1
Diphenoxylate	—	—	—	—	—	—
Etonitazene	Faint orange	1.0	—	—	Pale green	1.0
Furethidine	Faint orange	1.0	—	—	—	—
Hydromorphinol	Purple	0.1	Grey	0.1	Purple → blue → yellow	0.1
Levophenacylmorphan	Faint purple → grey → green	1.0	Grey-blue	1.0	Bright blue	0.5
Metazocine	Brown	1.0	Greenish-brown	1.0	Bright blue → green	1.0
Norlevorphanol	Olive	1.0	—	—	Blue → yellow-green	0.1
Phenampromide	—	—	—	—	—	—
dl-Phenazocine	Brown	1.0	Greenish-brown	1.0	Bright blue → green	1.0
l-Phenazocine	Brown	1.0	Greenish-brown	1.0	Bright blue → green	1.0
Phenoperidine	—	—	—	—	Faint grey-purple	1.0
Piminodine	—	—	—	—	—	—
R.951	—	—	—	—	—	—

Alkaloid	Selenious acid	Sensitivity (μg)	Sodium tungstate	Sensitivity (μg)	Vitalis test	Sensitivity (μg)
Allylprodine	Pale olive	1.0	Blue-grey	1.0	Yellow/yellow/grey → purple-brown	0.5
Benzethidine	Orange-brown	1.0	Faint grey	1.0	—/—/—	—
Clonitazene	—	—	—	—	Faint brown/faint brown/yellow-brown	1.0
Diampromide	—	—	—	—	—/—/—	—
Dimenoxadol	Orange	0.1	Orange → purple	0.1	—/—/grey	1.0
Diphenoxylate	—	—	—	—	—/—/—	—
Etonitazene	Yellow	1.0	Yellow-brown	1.0	Light brown/lt. brown/yellow-brown	1.0
Furethidine	—	—	—	—	—/—/—	—
Hydromorphinol	Green	0.1	Grey-purple	0.1	Yellow/yellow/orange	0.5
Levophenacylmorphan	Pale yellow	1.0	Black-purple	0.25	Yellow/yellow/orange	0.25
Metazocine	Brown	1.0	Grey-purple	1.0	Yellow/yellow/orange	1.0
Norlevorphanol	Yellow-brown	1.0	Black-purple	0.5	Yellow/yellow/orange	1.0
Phenampromide	—	—	—	—	—/—/—	—
dl-Phenazocine	Brown	1.0	Black-purple	0.1	Yellow/yellow/orange	1.0
l-Phenazocine	Brown	1.0	Black-purple	0.1	Yellow/yellow/orange	1.0
Phenoperidine	Faint brown	1.0	—	—	—/—/faint orange	1.0
Piminodine	—	—	—	—	Bright orange/yellow/orange	0.5
R.951	—	—	—	—	—/—/faint orange	1.0

Tranquillizing and related drugs: Properties for their identification (part II)

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Note by the editor: This part of the article is a continuation of part I, which was included in Volume XIII, No. 3, of the *Bulletin*.

Microscopic crystal tests

Crystal examination under the microscope is a rapid means of differentiating chemical compounds, and therefore a significant step in their identification. It requires small quantities of material, and utilizes relatively simple operations. The tendency to substitute for crystal tests such instrumental methods as spectrophotometry and vapour-phase chromatography does not diminish the value of the microscopic procedures for preliminary studies, which often lead to positive identification with minimum effort.

Starting with the historical work of Orfila (1), a pioneer in forensic toxicology, practically every common and many uncommon compounds, both organic and inorganic, have been identified by this approach. When performed by such techniques as that of Clarke (2), crystal tests provide not only ease of operation, but great reliability in their interpretation.

Fusion, sublimation and recrystallization tests from alcoholic and ammoniacal solutions were performed on 48 of the compounds listed in this study. Two or three of them have been reported previously (3). Most of the compounds were obtained in the pure crystal form, and extraction procedures were used to isolate seven of them from available prescription form.

Sublimation was performed by placing a few milligrammes of the compound in a depression of a cavity slide with a cover glass. The slide, placed on a melting point block, was heated gradually to a temperature of 250°C. Melting points were not determined.

Fusion was performed by heaping a bit of the compound on the corner of a glass slide and covering with a cover slip, after which the material was warmed by moving it slowly into the flame of a microburner. The temperature was increased until melting commenced, the slide being held in this position for a short while before being removed from the flame, to avoid overheating and decomposition. After cooling, the melt showed the presence of crystals in some instances, where the temperature gradient was established. In other instances there were variations of the form of the solidified melt.

Recrystallization from alcoholic solutions was performed with milligramme amounts of the compound to which were added, on a slide, a drop of 50% aqueous alcohol acidified with 6N hydrochloric acid. The compound was dissolved by stirring with a glass rod, warming over a microburner flame when necessary. The preparation was covered with a cover glass and allowed to cool and evaporate at room temperature. The solvent was not found suitable for some compounds, especially phenothiazine derivatives, for which 95% alcohol was used instead.

Recrystallization from ammoniacal solutions was obtained from concentrated ammonia solutions made similarly to the above description. In some instances a 50% alcoholic ammonia solution was used. Phenothiazine derivatives formed emulsions with ammoniacal solution, as also did the Rauwolfia group of alkaloids.

All preparations were photographed at 75X or 150X as indicated, and are shown in plates 1 to 6.

[1] This work was supported by grants from the National Institutes of Health, Public Health Service, Department of Health, Education and Welfare (RG-4372), and the Research Committee of the University of California. Acknowledgement is made to thirty manufacturers of tranquillizing drugs for supplying samples of their products.

Group A. — The phenothiazine derivatives

PLATES 1 *a*, 1 *b*, 1 *c*, 1 *d*

		Compound	I Sublimation	II Fusion	III Recrystallization from 50% alcohol : HCl
			Magnification		
Page 23, left					
Plate 1 *a*	Row 1	Promazine	150 ×	75 ×	150 × (95% alcohol)
	2	Promethazine	150 ×	75 ×	75 ×; 75 × (95% alcohol)
	3	Ethopropazine	150 ×	—	150 ×
	4	Trimeperazine	—	75 ×	150 ×
Page 23, right					
Plate 1 *b*	Row 1	Pyrathiazine	150 ×	—	150 × (95% alcohol)
	2	Chlorpromazine	150 ×	75 ×	75 × (95% alcohol)
	3	Prochlorperazine	150 ×	75 ×	150 ×
	4	Prochlorperazine-ethane disulfonate	—	75 ×	150 ×
Page 24, left					
Plate 1 *c*	Row 1	Prochlorperazine-dimaleate	150 ×	75 ×	150 ×
	2	Perphenazine	—	75 ×	75 × (95% alcohol)
	3	Thiopropazate	—	75 ×	150 × (95% alcohol)
	4	Triflupromazine	150 ×	75 ×	75 × (95% alcohol)
Page 24, right					
Plate 1 *d*	Row 1	Trifluoperazine	150 ×	—	150 × (95% alcohol)
	2	Fluphenazine	—	75 ×	75 × (95% alcohol)
	3	Methoxypromazine	—	75 ×	75 × (95% alcohol)
	4	Mepazine	150 ×	75 ×	75 ×

PLATE 1 *b*

PLATE 1 *a*

Group A. — The phenothiazine derivatives (*continued*)

PLATE 1 *c*

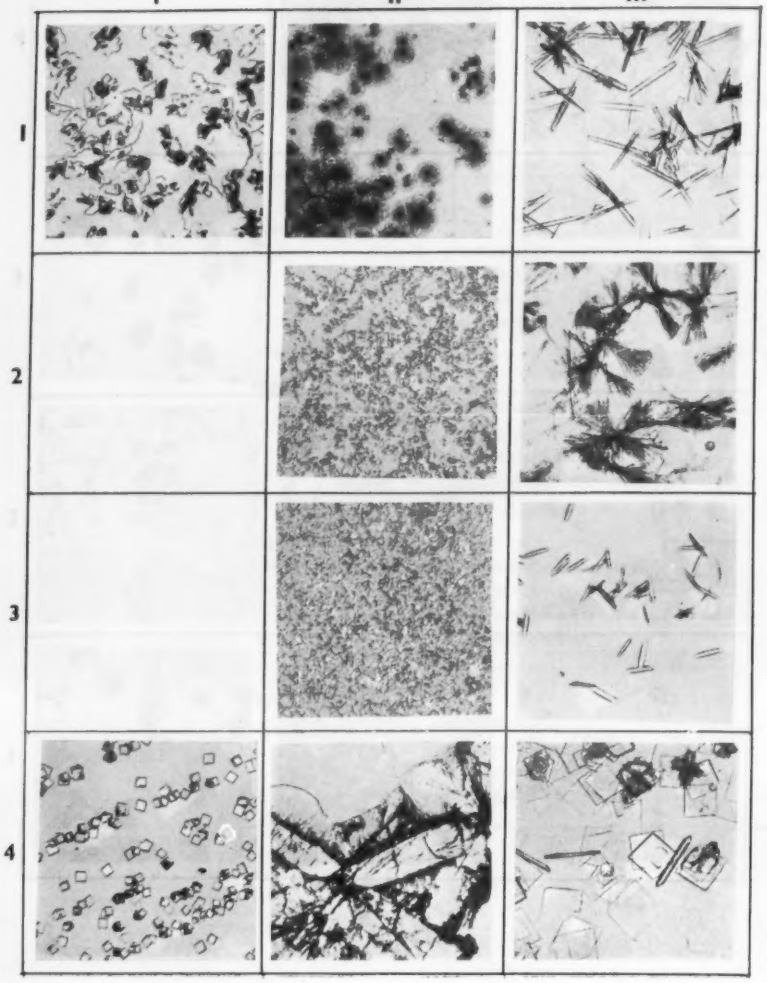
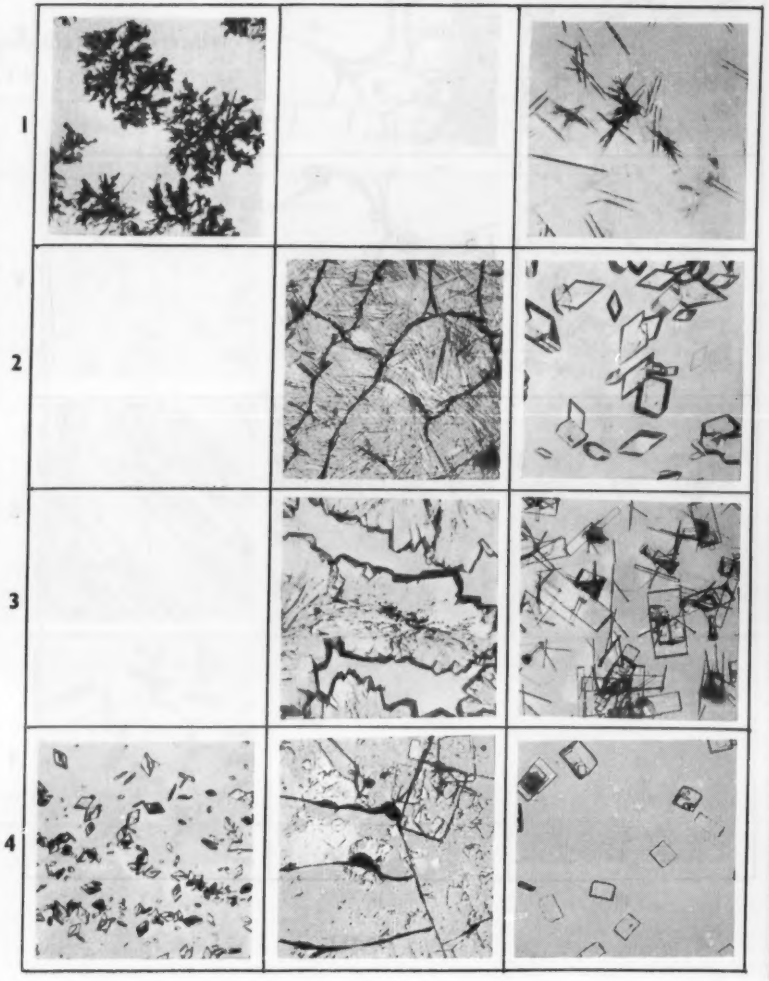


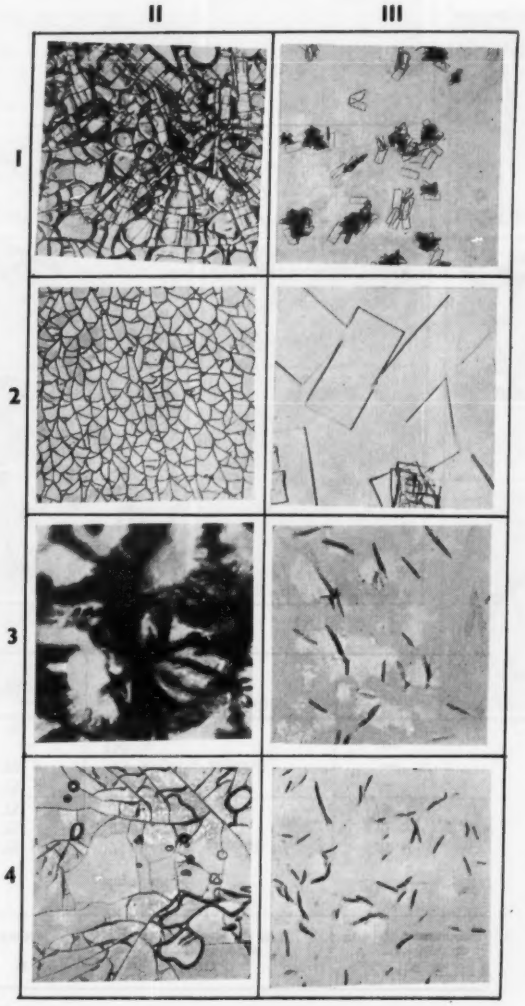
PLATE 1 *d*



Group B. — Reserpine and related alkaloids

PLATE 2

	Compound	II Fusion	III Recrystallization from 50% alcohol: HCl
		Magnification	
Row 1	Reserpine	75 ×	75 ×
2	Deserpidine	75 ×	75 ×
3	Rescinnamine ...	75 ×	150 ×
4	Alseroxylon	75 ×	150 ×



Group C. — The diphenylmethane derivatives

PLATES 3 *a*, 3 *b*, 3 *c*

		Compound	I Sublimation	II Fusion	III Recrystallization from 50% alcohol: HCl	IV Recrystallization from conc. ammonia
			Magnification			
Plate 3 *a*	Row 1	Adiphenine	—	75 ×	75 × (95% alcohol)	150 ×
	2	Diphenylpyraline	150 ×	75 ×	75 ×	150 ×
	3	Azacylonol	150 ×	75 ×	75 ×	75 ×
Plate 3 *b*	Row 1	Caprodiamine	—	75 ×	150 ×	—
	2	Chlorcylyzine	75 ×; 75 ×	75 ×	75 × (95% alcohol)	—
	3	Benactyzine	150 ×	—	150 ×	—
	4	Pipradol	150 ×	75 ×	75 ×	—
Plate 3 *c*	Row 1	Hydroxyzine	150 ×	—	75 × (95% alcohol)	—
	2	Meclizine	150 ×	75 ×	75 ×	—
	3	Buclizine	150 ×	—	75 ×	—

PLATE 3 *a*

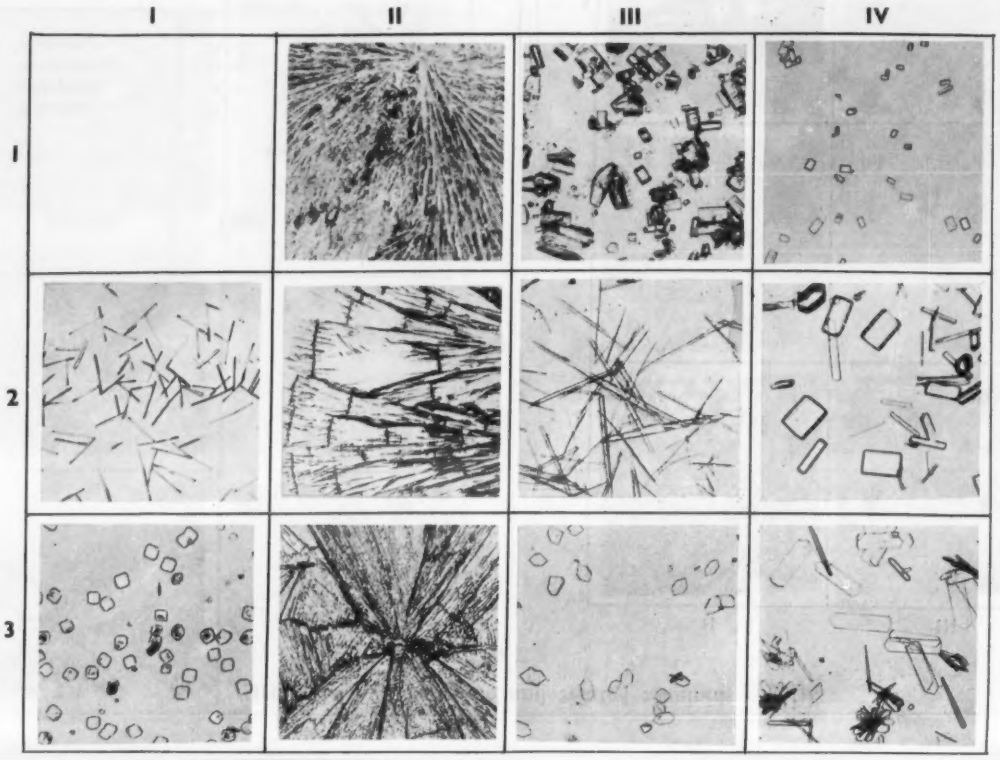


PLATE 3 *c*

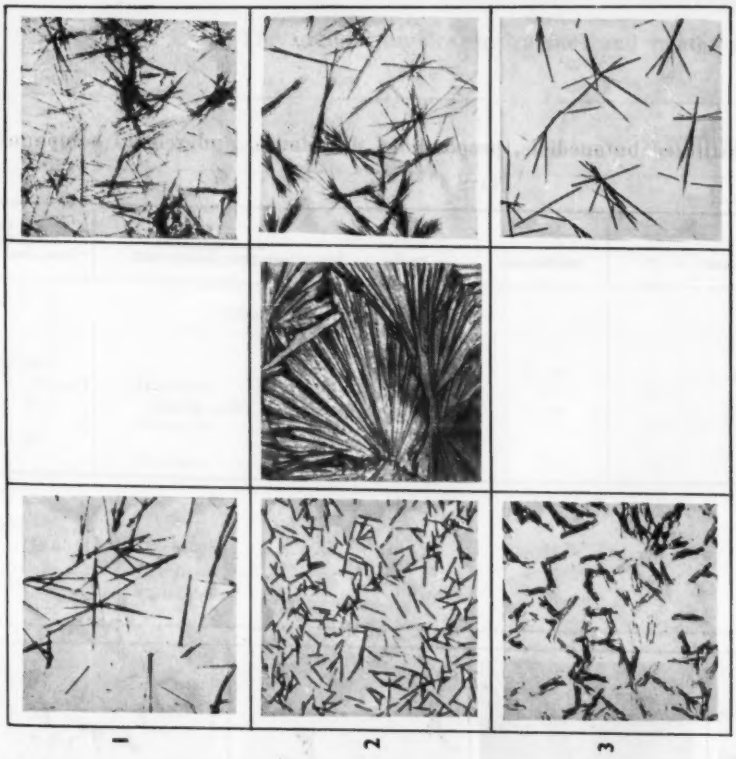
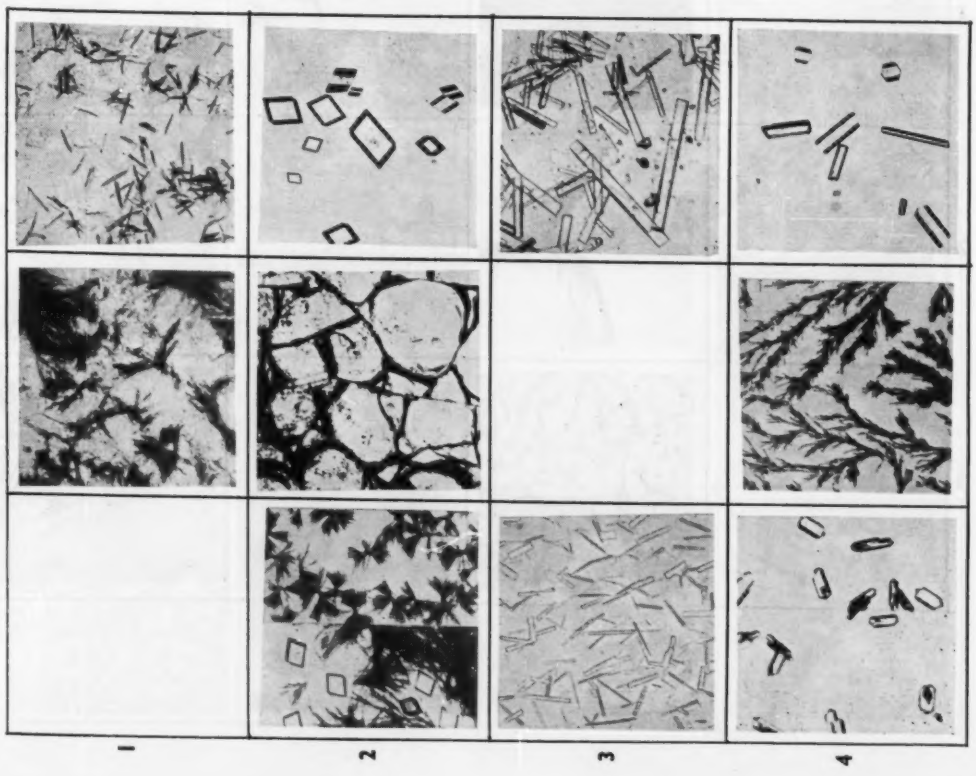


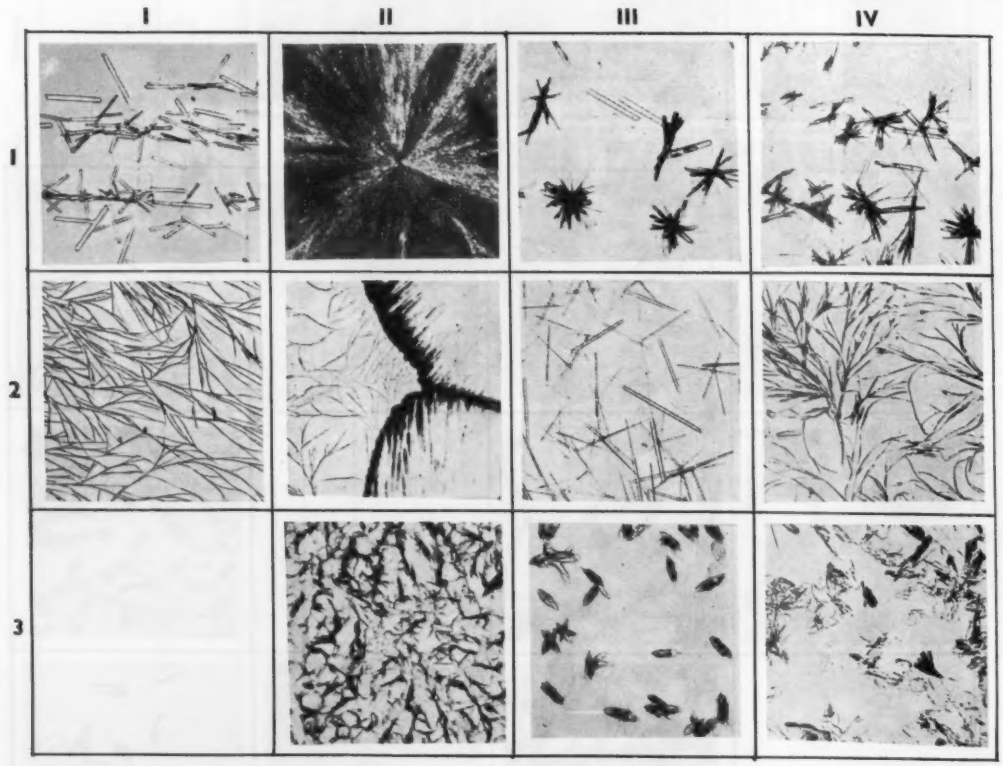
PLATE 3 *b*



Group D. — The substituted butanediols, propandiols, dioxalanes, and related compounds

PLATE 4

	Compound	I Sublimation	II Fusion	III Recrystallization from 50% alcohol; HCl	IV Recrystallization from conc. ammonia
		Magnification			
Row 1	Phenaglycadol.....	150 ×	75 ×	150 ×	75 ×
2	Mephenesin.....	75 ×	75 ×	75 × (95% alcohol)	75 ×
3	Meprobamate.....	—	75 ×	75 ×	75 ×



Group E. — The ureides, amides, hydrazines and related compounds

PLATES 5 *a* 5 *b* 5 *c*

	Compound	I Sublimation	II Fusion	III Recrystallization from 50% alcohol: HCl	IV Recrystallization from conc. ammonia
		Magnification			
Page 29					
Plate 5 *a* Row 1	Phenelzine	—	75 ×	75 × (95% alcohol)	150 ×
2	*a*-methylphenethylhydrazine	—	75 ×	75 × (95% alcohol)	150 ×
3	Isocarboxazide	150 ×	75 ×	150 ×	75 × (50 % alcohol: ammonia)
Page 30, upper part					
Plate 5 *b* Row 1	Iproniazid	—	75 ×	150 ×	75 × (50% alcohol: ammonia)
2	Nialamide	—	75 ×	75 ×	75 × (50% alcohol: ammonia)
3	Ectylurea	150 ×	75 ×	75 ×	75 ×
Page 30, lower part					
Plate 5 *c* Row 1	Oxonamide	150 ×	75 ×	75 ×	75 ×
2	Acetylcarbromal	150 ×	75 ×	150 ×	75 ×
3	Glutethimide	150 ×	75 ×	75 ×	150 ×

PLATE 5 *a*

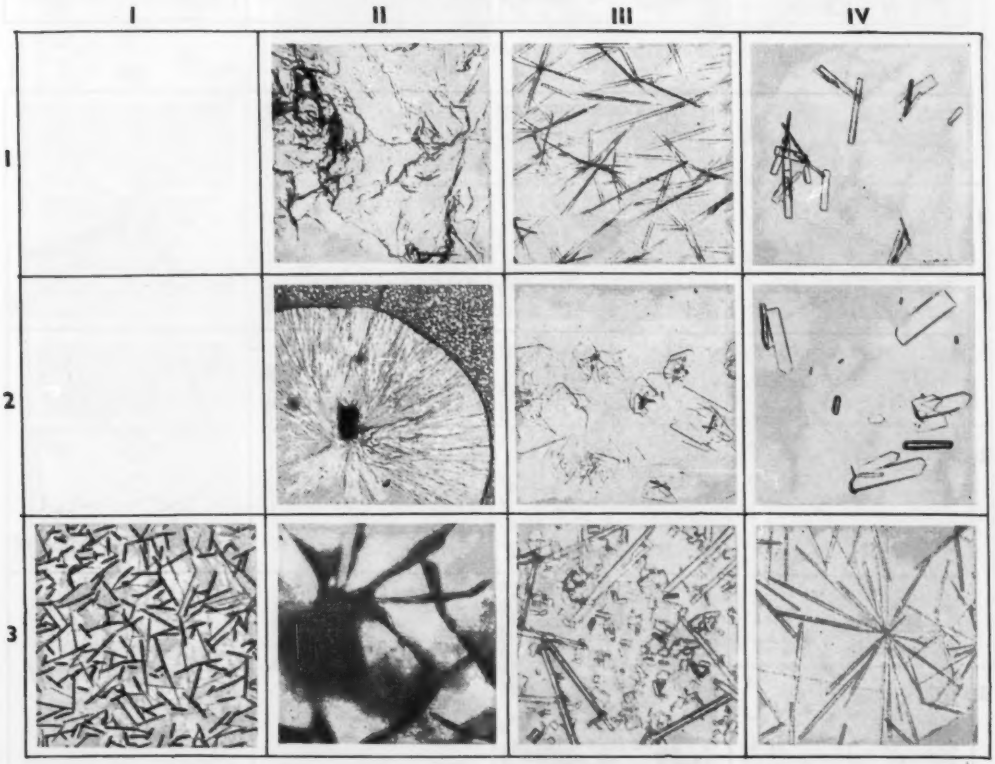


PLATE 5 *b*

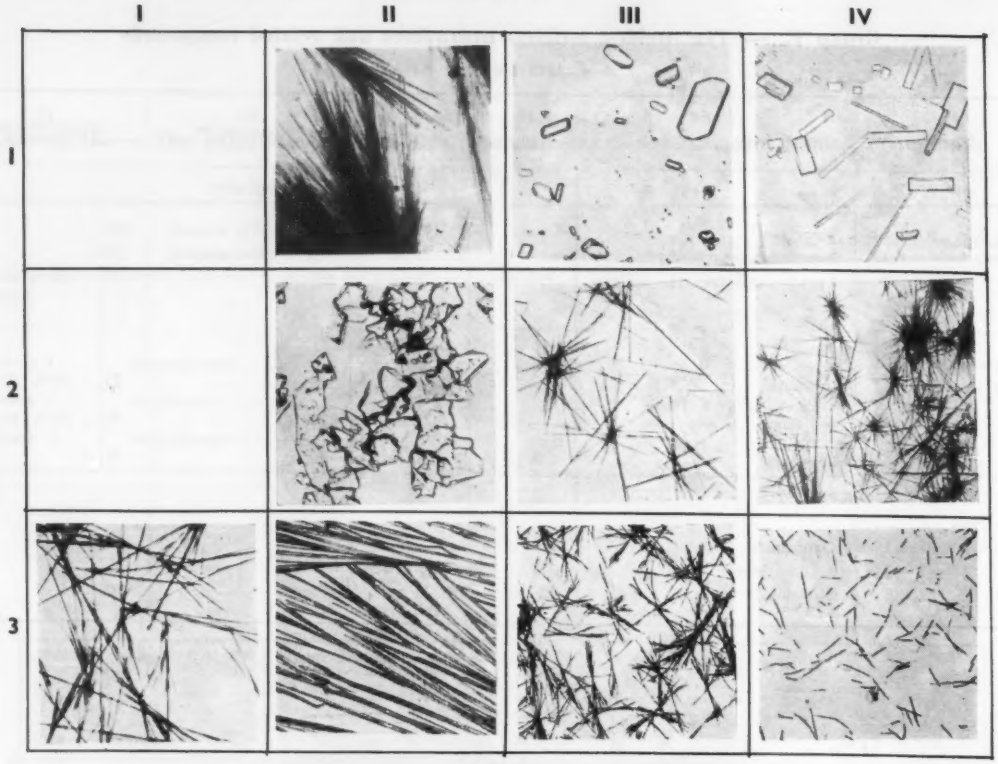
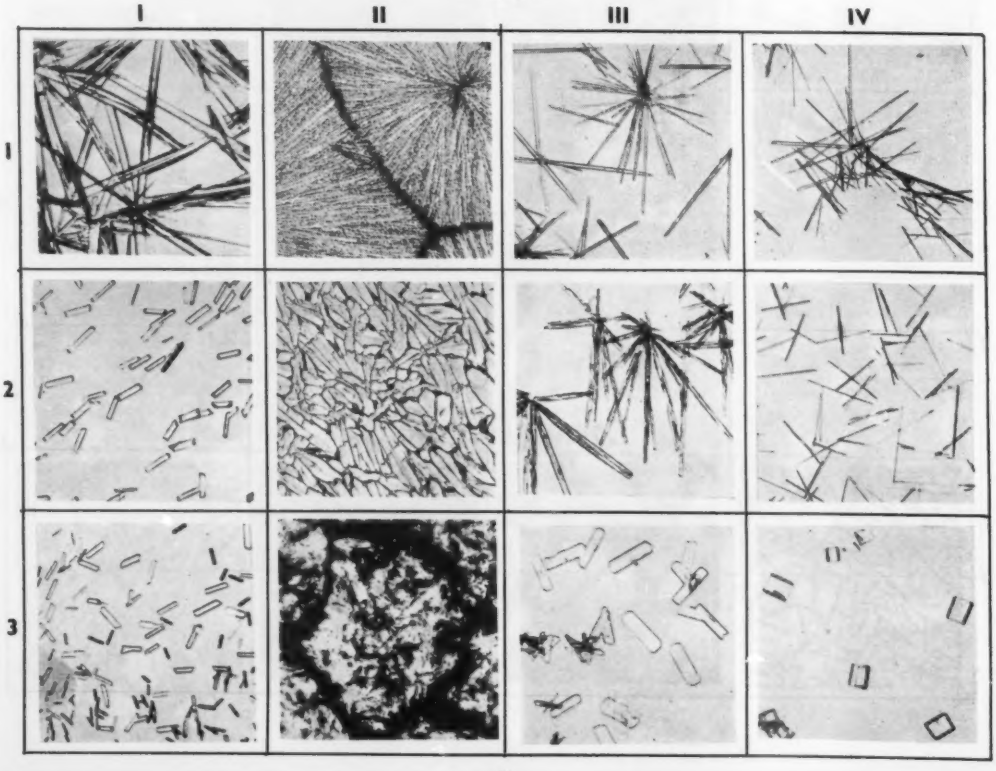


PLATE 5 *c*

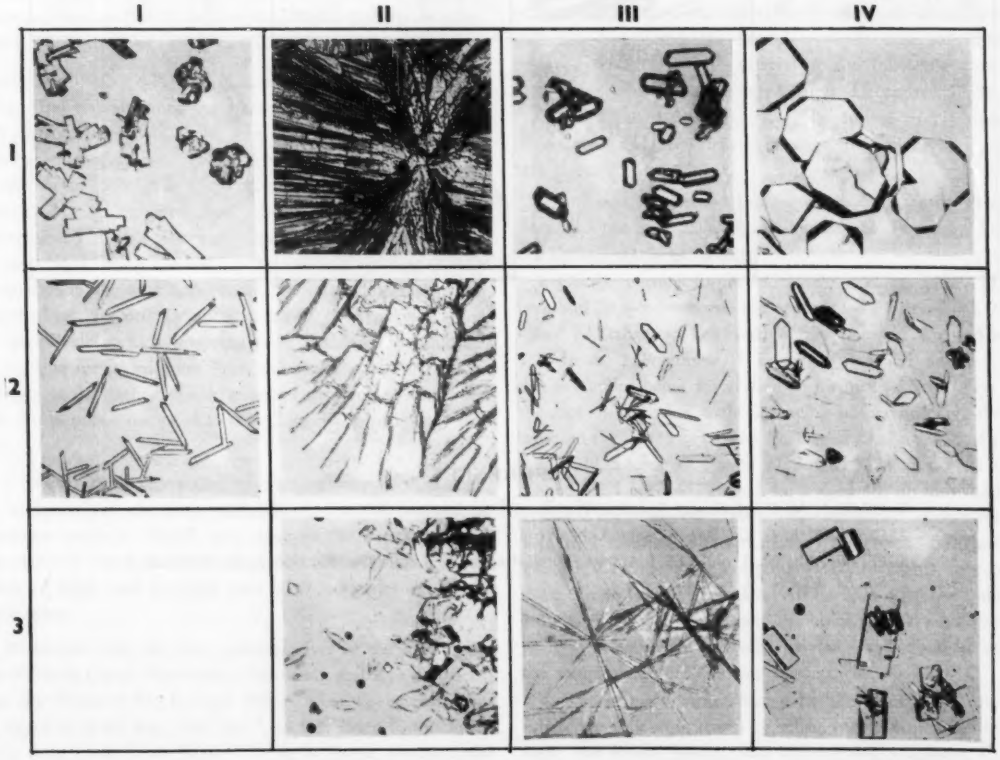


Group F. — Miscellaneous compounds

PLATES 6 *a*, 6 *b*

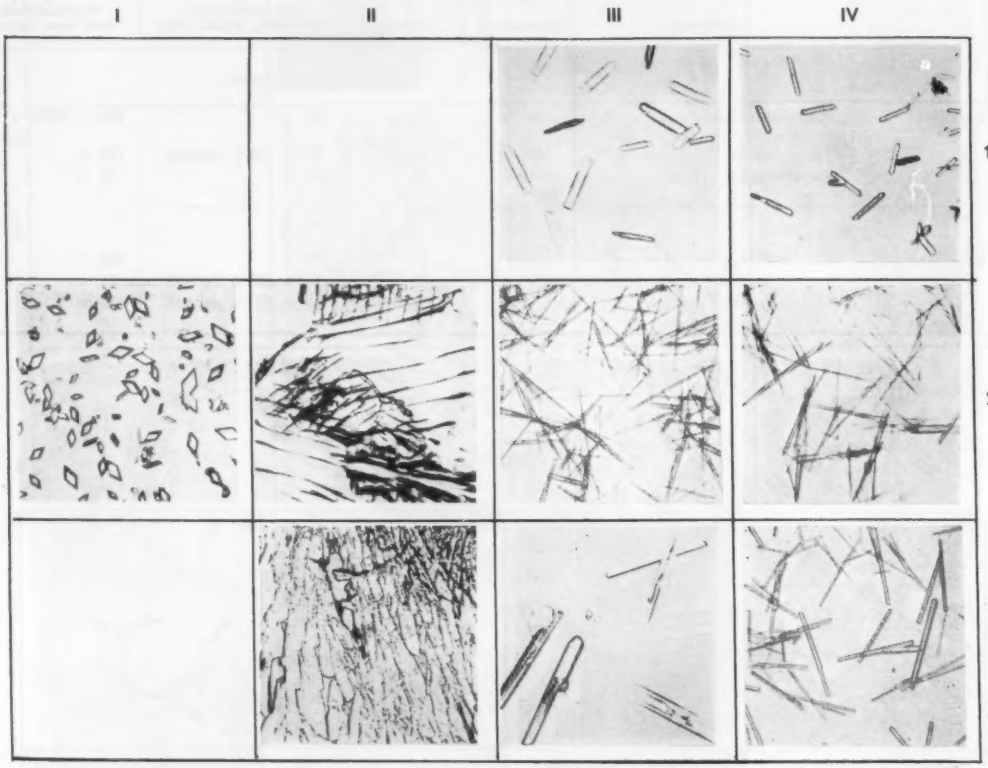
		Compound	I Sublimation	II Fusion	III Recrystallization from 50% alcohol; HCl	IV Recrystallization from conc. ammonia
			Magnification			
Page 31						
Plate 6 *a*	Row 1	Methylphenidate	150 ×	75 ×	150 ×	150 × (50% alcohol: ammonia)
	2	Thonzylamine	150 ×	75 ×	75 × (95% alcohol)	150 ×
	3	Pyrrobutamine	—	75 ×	150 ×	75 ×
Page 32						
Plate 6 *b*	Row 1	Chlormethazanone	—	—	150 ×	150 ×
	2	Imipramine	150 ×	75 ×	75 × (95% alcohol)	75 ×
	3	3-(β-aminoethyl) pyrazole.....	—	75 ×	150 × (95% alcohol)	150 ×

PLATE 6 *a*



Group F. — Miscellaneous compounds *(continued)*

PLATE 6 *b*



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Data on the illicit traffic in cocaine and coca leaves in South America, with an annex on narcotics control in Brazil

By Dr. Decio Parreiras

President of the Brazilian National Commission for the Control of Narcotic Drugs; Member of the Permanent Central Opium Board and the Drug Supervisory Body

On 25 September 1956, the Brazilian Government was informed by telegram from Lima of the existence of an illicit traffic in cocaine and coca leaves between Brazil and Peru. The traffic was made easier by the inadequacy of local policing in the vast mountain region where the two countries meet.

It was said that the smugglers had large financial resources, expert technicians and abundant equipment for manufacturing cocaine. It was even acknowledged that there was a large factory on the Amazon plateau and that the traffic was mainly between the towns of Iquitos in Peru and Manaos in Brazil. From there, the drug was sent to Rio de Janeiro, São Paulo and Paramaribo, whence it reached Cuba, Mexico and Italy.

As early as 12 June 1957, the diplomatic representative of Brazil at La Paz (Bolivia) informed the customs inspector of Corumba (Brazil) that the Bolivain Government had discovered clandestine laboratories manufacturing cocaine, which was smuggled to São Paulo by air. It was therefore considered necessary to search all parcels, luggage, cameras and hand-bags systematically. He mentioned 29 large-scale smugglers already known to the Bolivian police who were using aircraft of the national air line (CAS). In January 1958 the attention of the National Commission for the Control of Narcotic Drugs was drawn to what was going on in São Paulo, which now has over 3 million inhabitants, where cocaine smuggled from Peru and Bolivia was being sold quite freely in the night-clubs. In several raids made at that time, the São Paulo police managed to seize 2 kg 800 g of illicitly sold cocaine.

On 1 March 1958, the police of the province of Amazonas began to investigate the drug traffic in the city of Manaos, in the extreme north of Brazil, and came to the conclusion that all the alkaloid seized had been manufactured in Bolivia, in the province of Beni, and brought into other countries across the Amazon river.

On 28 March 1958, the four representatives of the state police forces of Minas Gerais, São Paulo, Guanabara and Rio de Janeiro met at the Ministry for Foreign Affairs (Rio de Janeiro) and, with regard to what was called the " cocaine route ", concluded that the drug came from Santa Cruz de la Sierra, Cochabamba and Sucre (Bolivia), that it was passed on to Corumba (Mato Grosso, Brazil) and that from there it went to São Paulo and Rio de Janeiro, mainly by air, thus reaching the two principal centres of consumption in South America.

By that time, however, the police of Rio de Janeiro and São Paulo already knew the trafficker's exact route and had placed in custody on criminal charges the internationally known leaders of the gang — namely: Mario Caso, Jose Kathoumi, Jorge Skeff, Capitro Pablo Arias Ortiz (known as "Pablito"), Ricardo Caponi, Julio García, and others.

Initial statistics

The technical staff of the National Commission for the Control of Narcotic Drugs — the federal body which, in Brazil, is responsible for supervising the lawful trade in narcotic drugs and combating illicit traffic — arrived at the following conclusions during the period September 1956 to December 1959:

1. A total of 163 persons were implicated in the smuggling of cocaine and coca leaves between nine American countries and Italy.

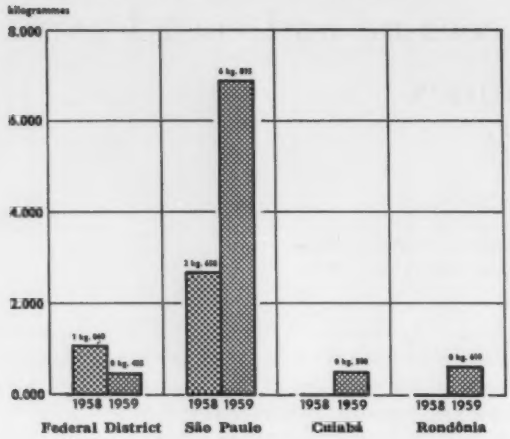
2. The nine American countries concerned were: Argentina, Bolivia, Brazil, Chile, Cuba, Dutch Guiana, Paraguay, Peru and the United States of America.

3. Of the persons implicated in the cocaine traffic, 143 were men and 20 were women; they comprised 54 Brazilians, 24 Bolivians, 12 Italians, 5 Lebanese, 4 Egyptians, 1 North American, 1 German, 1 Portugese, 1 French, 1 Japanese and 1 Chilean, the remainder being impossible to identify; sixteen were white, the race of the other traffickers being unspecified save that there were no negroes; 1 was aged 19, 1 aged 23, 2 aged 25, 3 aged 27, 2 aged 29, 5 aged 30, 1 aged 34, 2 aged 35, 1 aged 37, 1 aged 38, 3 aged 39, 1 aged 41, 1 aged 45, 1 aged 48; no information was available regarding the others. They included 1 aircraft mechanic, 1 pilot, 1 chemist, 2 pharmacists, 4 tradesmen, 1 manufacturer, 1 singer, 4 car drivers, 1 policeman, 2 civil servants, 1 ex-ambassadress, 2 members of the Federal Air Force, 1 doctor of philosophy, 1 domestic servant, 1 hawker, 1 cobbler, 1 motor-car parts salesman, 21 unemployed; 10 were married, 7 single and 1 a widower, the status of the others being unspecified.

4. The country most affected by the illicit traffic was Brazil, where the following towns or villages were visited by the traffickers: São Paulo, Santos, São Vicente, Itu, Caçapara, Corumba, Cuiba, Aquidauana, Fazenda do Mandiore, Esplanada, Vila Bela, Campo Grande, Fazenda do Pantanal, Porto Pinasco, Coxim, Ponta Pora, Manaos, São Paulo de Olivença, the Amazon forests, the banks of the river Solimoès, Belem, Porto Velho, Guajara-

FIGURE 1. — Quantities of cocaine seized

In 1958: 3 kg 718 — In 1959: 8 kg 460



Mirim, Paqueta Island, Rio de Janeiro, Goiania, Nova Friburgo, Caxias and Belo Horizonte. Bolivia came second, the following towns or villages being affected: La Paz, Santa Cruz de la Sierra, Roborá, Cochabamba, and Sucre; in third place was Peru, where the traffic centred in Iquitos, Lima, Fazenda Upuni, Urucefia, and Camiri;

5. During the period considered, the police of Guanabara, Mato Grosso, São Paulo and Rondonia Territory seized 12 kg 179 g of smuggled cocaine — an amount four times greater than that seized in the United States of America, which was 3 kg 164 g; this works out at 196 g of the drug per thousand inhabitants in Brazil, as compared with 19.5 g per thousand in the United States. These facts speak for themselves.

Repercussions in the international control bodies

On 5 March 1959 the Brazilian Government informed the Secretary-General of the United Nations of the gravity of the situation; there was an immediate and strong reaction to the Brazilian announcement, in particular by the Commission on Narcotic Drugs of the Economic and Social Council at its fourteenth session, held at Geneva from 27 April to 15 May 1959.

In document E/3254, the Commission draws attention to Brazil's annual report for 1957-1958, refers to the situation also existing in Cuba, Argentina, Bolivia, Paraguay and Peru, and expresses its concern at the absence of full co-operation between the national authorities responsible for combating the illicit traffic.

The Commission suggested that the governments of Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, Paraguay and Peru should combine their efforts and work in co-operation with the international bodies concerned.

The Brazilian Government accepted this suggestion, and convened the Rio de Janeiro Conference, which was held from 21 to 25 March 1960.

Problems of the production and export of coca leaves

In its report for 1959 (document E/OB/15), the Permanent Central Opium Board states that the production of coca leaves for chewing is large and that it is the major cause of an international illicit traffic in them, which also serves to supply the clandestine manufacture of cocaine.

According to the Board, the amounts of coca leaves used for chewing between 1954 and 1957 were as follows (in tons):

	1954	1955	1956	1957	Total
Peru	9,250	9,319	9,450	9,954	37,973
Bolivia	2,764	?	?	2,950	?
Argentina	129	155	14	152	450
Colombia	110	100	80	32	322

Argentina, which is included in the above table, is a very small producer of coca leaves, and imports them only for a small group of workers on the northern frontier. The position is the same in Brazil, Chile, Ecuador, Paraguay, Venezuela, Cuba and Mexico, where little or none is grown.

As can be seen from the above table, coca leaf chewing is fortunately decreasing, since it has not increased in proportion to indigenous population growth in the four countries mentioned.

The Rio de Janeiro Conference

The Inter-American Conference on the Illicit Traffic in Cocaine and Coca Leaves met from 21 to 25 March 1960 at the Itamarita Palace (Ministry for Foreign Affairs). It was attended by the Director of the United Nations Division of Narcotic Drugs, by the Assistant Secretary-General of Interpol, and by representatives of Argentina, Bolivia, Chile, Colombia, Cuba, Ecuador, Brazil, Mexico, the United States of America, Venezuela, Paraguay and Peru. Extensive work was done to secure mutual co-operation between a number of neighbouring or adjoining countries.

It must be recognized that the measures taken were so successful that seizures of smuggled coca leaves and cocaine in 1960 fell to almost nil. There is every reason to believe that the delegations of the two cocaine producing countries made a most effective approach to their respective governments, which closed down the clandestine laboratories producing the smuggled cocaine.

ANNEX

Brazilian Legislation in Force

It must be pointed out that existing Brazilian legislation gives the police and health authorities wide powers to combat illicit traffic in narcotic drugs anywhere in the country.

Article 1 of decree No. 780 of 28 April 1936 established the National Commission for the Control of Narcotic Drugs, which since that time has been responsible for studying and drawing up general rules for the cultivation, extraction, production,

manufacture, processing, preparation, possession, import, offer, sale, purchase, exchange and transfer of narcotic drugs and for combating illicit traffic and illicit use.

The National Commission for the Control of Narcotic Drugs has its headquarters in the capital of Brazil at the Ministry for Foreign Affairs, and is under the direct authority of the Minister of State. It is composed of representatives of the ministries of justice, labour, war, marine, health and customs, and two or three technical experts.

Subordinate to the National Commission for the Control of Narcotic Drugs, there are 21 State Narcotics Control Commissions, which operate in the different states of the union, and each consists of 5 members — namely, the Director of Public Health of the State, the regional attorney, a representative of the National Health Department, a representative of the medical profession of the state capital, the Director of the State Medicine and Pharmacy Control Department, and the head of the police department or his representative, who is generally the narcotics officer.

It must be added that the network of subordinate authorities for combating illicit traffic in narcotic drugs includes 21 administrative units — namely, the 21 state police authorities coming under the federal police department, which makes a total of 220 officials mainly concerned with narcotics.

When the existence of an illicit traffic in a particular drug is established, the National Commission and the State Commissions co-ordinate their activities and call on the services of the local police, as was done in connexion with the recent cocaine smuggling.

Offences and Penalties

Articles 33 to 40 of decree law No. 891 of 25 November 1938 provide that anyone who facilitates the acquisition, use or administration of any narcotic substance, or who, without complying with the prescribed legal formalities, sells, gives, retains, carries, sends, or exchanges narcotic drugs, shall be liable to a term of imprisonment of one to five years and to a fine of up to 5,000 cruzeiros.

If the accused is a pharmacist, his right to practise his profession may be suspended for a period of 3 to 6 years. If he is a doctor, dentist or veterinary surgeon, the period of suspension may be 4 to 10 years.

Suspended sentences and conditional release are not granted in the case of the above-mentioned offences.

Internment and Loss of Civil Rights

During the present campaign against smuggling and illicit traffic in cocaine from Bolivia and Peru, it has been found that the smugglers are not generally drug addicts. Only five traffickers have shown obvious symptoms of addiction.

In cases of addiction, Brazilian legislation requires:

(*a*) Compulsory confidential notification of the local health authorities;

(*b*) Refusal to treat the addict at home;

(*c*) Admission to a hospital, which may be compulsory or optional according to the circumstances.

Compulsory hospitalization can be carried out only on an order of the court, when it is shown that proper treatment in a hospital is necessary or is in the public interest. A judicial decision is required in all cases.

Loss of civil rights may be partial, in which case it corresponds to relative incapacity, or complete, when it corresponds to total incapacity, in accordance with articles 5 and 6 of the Civil Code.

Narcotics Register

The purpose of control over the issue of medical prescriptions for the use of narcotic drugs is to prevent drug addiction and the illicit sale of narcotics.

Brazilian law now provides that pharmacies may only make up such prescriptions if they are signed by a doctor whose qualifications are duly registered; that the prescriptions must first have been seen by the competent health authorities; and that they must be written on official forms and give reasons for the use of the drug. Such prescriptions may not be repeated until 48 hours have elapsed and they may not be repeated over a period of more than seven days.

Members of a profession who use their qualifications in order to prescribe or administer narcotic drugs improperly may not be supplied with the official forms for prescribing such drugs. The facts must be notified to the police authorities, and where criminal responsibility is established the offenders are liable to a term of 3 to 10 years' imprisonment, a fine of 3,000 to 10,000 cruzeiros and suspension of their right to practise for 4 to 10 years.

Regional Conferences of Narcotics Police

With a view to co-ordinating the efforts and combined action of the state police authorities in the areas where the illicit traffic in cocaine and other narcotic drugs is greatest, the National Commission for the Control of Narcotic Drugs has been organizing seminars in various states of Brazil.

The first of these conferences was held at Rio de Janeiro in 1958, in the Itamarati Palace, and was attended by representatives of the narcotics departments of Rio (Guanabara State), Minas Gerais, São Paulo and Rio de Janeiro State. Doctors from the health delegations of five Brazilian states were also present at the meeting.

The second conference of narcotics police was held at São Paulo on 8 and 9 May 1959. In addition to nearly all the members of the National Commission for the Control of Narcotic Drugs, it was attended by representatives of the special branches of Rio de Janeiro, São Paulo, Rio de Janeiro State and Minas Gerais, which have the best police organizations in Brazil and which, by reason of their area and population density, have the greatest number of traffickers in cocaine, cannabis and opium derivatives.

Special Police

At these meetings between neighbouring states, the National Commission for the Control of Narcotic Drugs pointed out that traffickers show no respect for municipal, state, national or international frontiers, and it was shown that immediate steps were required to combine the action taken by the various state and municipal police authorities, who by themselves could achieve

nothing in the campaign to wipe out the medico-social scourge of drug addiction.

Another point continually stressed by the Commission is the urgent need to recognize the highly specialized nature of the departments responsible for combating the misuse of toxic substances, so many of which are now available in the pharmaceutical trade.

As was pointed out at the important Inter-American Conference on the Illicit Traffic in Cocaine and Coca Leaves, held at Rio de Janeiro from 21 to 25 March 1960, in such a specialized field, one cannot go on relying on the work of technical staff improvised at a moment's notice, the continuity of which is most uncertain in the field of narcotic drugs. Above all, there is an urgent need for the technical assistance so strongly recommended by the Economic and Social Council of the United Nations.

International Co-ordination

The Interpol authorities rightly emphasize the value of enforcement staff in combating traffic of a local character; but they also point out that it is well known that the illicit traffic has an international aspect, which is the most dangerous one.

Hence the need for team-work, and for permanent co-operation between the federal police services of each country or territory, since frontiers do not always constitute a serious obstacle to the criminal activities of the offenders. There is therefore an imperative need for thorough technical documentation, information and co-ordination centres in the various regions, international card indexes classified in alphabetical order, and indexes of finger prints, photographs, personal descriptions and particulars of offenders. To this end, it is also essential to keep up-to-date statistics of drug consumption, numbers of addicts, sentences passed on traffickers and the volume and nature of contraband discovered.

Frequent personal contacts are of vital importance for effective action against drug traffickers.

Educational Literature

The National Commission for the Control of Narcotic Drugs has been publishing at regular intervals a series of educational monographs, which are distributed free of charge in Brazil and the Spanish-speaking countries. They comprise the following:

(1) Brazilian cannabis (A few notes)
(2) Commentary on Brazilian legislation on the trade in, therapeutic use of, and illicit traffic in narcotic drugs
(3) Texts of Brazilian legislation in force on narcotic drugs
(4) Second conference of narcotics police
(5) Regulations for the registration and sale of narcotics
(6) Confidential report of the Brazilian delegation to the Inter-American Conference on the Illicit Traffic in Cocaine and Coca Leaves
(7) Census of drug addicts in Brazil
(8) List of narcotic drugs under international control
(9) Final Act of the First Inter-American Conference on the Illicit Trafic in Cocaine and Coca Leaves
(10) Licit consumption of narcotic drugs; situation of Brazil and South America.

The South-East Asia Consultative Group on Narcotics Control

Bangkok, December 1960

Over a number of years, information presented by governments to the international bodies has indicated a large-scale narcotics problem in the region of South-East Asia. The region has an indigenous production of opium, which supports both a large amount of addiction within the region and a heavy traffic to other parts of the world. In recent years, illicit morphine and heroin production and heroin addiction have appeared on a significant scale. It has become clear that an opium problem which is not mastered can become transformed into a major morphine/heroin problem in the relatively short space of a few years. The realization of this latter danger on the one side, together with encouraging progress in work in the region on enforcement questions and treatment facilities for addiction on the other, was considered to make an exchange of experience useful and timely.

The South-East Asia Consultative Group on Narcotics Control was arranged by the United Nations as part of the special supplementary programme of technical assistance in narcotics control provided for in General Assembly resolution 1395 (XIV). It met in Bangkok for two weeks in December 1960, with the Government of Thailand acting as host country. The group consisted of senior officials from Burma, Cambodia, Federation of Malaya, Hong Kong, Laos, Macao, Singapore and Thailand, nominated by their governments to participate as individual experts. Observers from the WHO and the ICPO also attended. Dr. H. A. Azarakah, Director-General, Department of Narcotics Control, Iran, and Mr. H. G. Christie, Canada, acted as consultants; and regional representatives of the FAO and WHO, as well as of the Economic Commission for Asia and the Far East, participated in some of the discussions. During the meeting the Government of Thailand made arrangements for the group to visit (i) frontier areas and posts in the north of Thailand; (ii) an experimental settlement for hill tribes, and (iii) the Rangsit Centre for Addicts.

While the detailed proceedings of the group are, in accordance with the usual practice in technical assistance projects, confidential to the governments concerned, there are some points of general interest which arose at this meeting.

The meeting of the group was designed to examine the current situation as regard narcotics problems in this region, to explore what action was desirable and practicable to improve it, and to make suggestions for the consideration of governments. The group recognized that a complete anti-narcotics policy would comprise enforcement measures, facilities for treatment and rehabilitation of addicts; educational measures, and, in countries where there was cultivation of the opium poppy, appropriate social and economic, including agricultural, measures.

Under the heading of enforcement, the group discussed, among domestic questions, the co-ordination of enforcement services; policy of rewards to members of the enforcement services and of rewards to informers; intensification of control at seaports and airports as nodal communications ports, with special reference to the " ships' watch " system as developed in Hong Kong; and the various questions connected with training.

The discussion on international co-operation on enforcement in the region centred mainly round four topics: bilateral co-operation in control of land frontiers, joint arrangements to investigate the increasing morphine traffic, the scheme for the determination of the geographical origin of opium by physical and chemical methods, and the general question of the degree of institutionalization of regional co-operation in the region, including exchange of information. Special attention was given to the possibilities of frontier agreements.

Regarding treatment facilities, the group discussed the experience gained of the various facilities for this purpose already existing in the region; the significance for the region of the distinction between " social " or " accidental " addicts as compared with addiction associated with personality problems or defects; the medical approach to addiction; and the possibilities of training personnel for the treatment services both inside and outside the region itself.

The group considered that the social climate, or prevailing social attitudes to addiction and to the illicit traffic, was of first importance, especially in transitional periods when governments are trying to carry through reforms within a relatively short period. The use of various media, as well as the possibilities of utilizing various organized groups, such as religious bodies, the medical profession, and voluntary organizations, were discussed.

As regards cultivation of the opium poppy, the group considered the scope of the problem in the region. In the Shan States of Burma, production for local consumption is legal. In northern Laos and in some other similar areas also, opium cultivation is part of the customary economic and social structure of some of the tribes, and administrative means of control are largely lacking, owing to lack of communications and the prevailing state of insecurity. Illicit opium also enters the region over the northern frontiers. The indigenous production of opium is at once the aspect of the problem on which least progress has been made and the most difficult to tackle, but also the essential long-term key

to the regional programme as a whole. While this production lasts on anything like its present scale, measures in the other sectors, enforcement, treatment, education, etc., cannot be more than more or less successful containment actions. Further, they will remain extensive and costly operations for governments as long as large supplies of opium are available in the region, and the situation will remain subject to the danger of regression, and indeed of rapid regression. The group was in general agreement that, in spite of the very great difficulties, all encouragement should be given to governments to do as much as possible to initiate or extend action in this sense, in their own long-term interest as well as that of the international community. In this context, the group discussed the effect of certain schemes which some governments had initiated on broader policy grounds, notably resettlement of hill tribes (Thailand, Laos, Viet-Nam) and educational and welfare teams working in formerly unadministered territories (Burma); other relevant experience, particularly that of Iran; indications regarding the quantitative aspects of the problem, for which surveys would be required; and the extent to which the cultivators as compared with intermediaries in the opium traffic would be affected by changes in the agricultural economy. The group thought that it was not practicable to tackle the opium element in the situation in isolation. The level of living, and particularly the agricultural economy, of the tribes have to be developed as a whole, at the same time as elements of normal administration are progressively introduced. What is feasible and necessary is that, within this process, special attention should be given to the opium factor. Besides agricultural development, it was the view of the group that community development techniques, combining as they do work on the various sectors of economic and social development, might well play a most useful part. They could be readily combined with schemes for agricultural development, educational measures, and establishment or improvement of health and welfare services in the areas concerned. They could be particularly valuable in setting an example which might give rise to spontaneous emulation in neighbouring valleys and so expedite the whole process. It was felt, however, that the type and scale of assistance available under the existing programmes of technical assistance of the United Nations and specialized agencies, while useful as a beginning, were not commensurate with the magnitude of the effort that would be required to get a radical solution of the problem of opium cultivation under way. Indeed, if such initial work was not to lead to disappointment and frustration, it was necessary to predicate assistance on a large scale — at least on the scale available under the United Nations Special Fund.

The group discussed the standard forms of technical assistance, and made a number of suggestions as to country projects for consideration by the governments concerned. It also suggested that governments might wish to give consideration to a programme, over the next several years, of certain inter-country or regional projects, mainly (i) a study-tour of seaports and airports in the region; (ii) inter-country investigation of the morphine traffic; (iii) further meetings of " consultative groups " of senior officials to make suggestions on policy at appropriate intervals; (iv) regional training in connexion with (*a*) enforcement work, (*b*) treatment facilities; (v) an interregional — rather than regional — seminar on methods of treatment, organized by the World Health Organization.

The sixteenth session of the Commission on Narcotic Drugs, and the thirty-second session of the Economic and Social Council

The Commission on Narcotic Drugs met in Geneva from 24 April to 10 May 1961, and the Economic and Social Council met in Geneva from 4 July to 4 August 1961.

The Commission elected as officers:

Chairman: Mr. K. C. Hossick (Canada)

First Vice-Chairman: Mr. M. Ozköl (Turkey)

Second Vice-Chairman: Mr. A. Ismail (United Arab Republic)

Rapporteur: Dr. J. Mabileau (France)

Mr. T. C. Green (United Kingdom) was elected Chairman of the Committee on Illicit Traffic.

The Commission and the Council discussed, *inter alia*, the following items.

Plenipotentiary Conference for the Adoption of a Single Convention on Narcotic Drugs

In accordance with Council resolution 689 J (XXVI), the Secretary-General convened a plenipotentiary conference for the adoption of a single convention to replace the existing multilateral treaties on narcotic drugs. Seventy-three States participated in the conference, which was held at United Nations Headquarters in New York, 24 January to 25 March 1961, and one further State was represented by an observer. Six intergovernmental organizations and three nongovernmental organizations were also represented. In addition, General Safwat, the Director of the Permanent Anti-Narcotics Bureau of the League of Arab States, attended in a personal capacity at the invitation of the conference. The conference elected Ambassador Carl Schurmann, the representative of the Netherlands, chairman, and the representatives of the following countries vice-presidents: Afghanistan, Brazil, Dahomey, France, Hungary, India, Iran, Japan, Mexico, Pakistan, Peru, Switzerland, Thailand, Turkey, Union of Soviet Socialist Republics, United Arab Republic, United Kingdom, United States of America. The conference adopted a Single Convention on Narcotic Drugs, 1961 (document E/CONF.34/22), and a Final Act (document E/CONF.34/23), to which are annexed five resolutions dealing with technical assistance, treatment of drug addicts, illicit trafficking, membership of the Commission on Narcotics Drugs and international control machinery, the latter two being directed to the Council. The convention will, in accordance with its article 41, come into force on the thirtieth day following the date on which the fortieth instrument of ratification or accession is deposited, in accordance with article 40.

While there were the inevitable differences inherent in such a large conference between what was hoped for and what was practicable, these were largely resolved by mutual compromises and the conference was able substantially to achieve the three main tasks which Council resolutions 159 II D (VII) and 246 D (IX) had prescribed for it. First, the codification of the existing multilateral treaty law in this field was almost completely achieved, with the exception that the convention of 1936 for the suppression of the illicit traffic in dangerous drugs would generally be continued as between the parties to it who wish to do so. However, as the 1936 convention had not been widely ratified, this relatively small exception from a complete codification into a single document was justified on the grounds that some States, among whom are those important for purposes of narcotics control, will, under the new convention, be able to accept some obligations which under the 1936 convention they had not been able to assume on account of the incompatibility of this convention with some basic principles of their legal systems; at the same time, those States which are willing to apply the stricter provisions of the earlier treaty will still be free to do so. The second main aim — the simplification of the international control machinery — was achieved by the joining together of the Permanent Central Opium Board and the Drug Supervisory Body into a single body with some supporting administrative simplifications. As regards the third task, the extension of the control system to the cultivation of plants grown for the raw materials of natural drugs (opium, cannabis and coca leaves), a new and definite provision to limit harvesting of opium, cannabis and cannabis resin and generally also of coca leaves exclusively to medical and scientific purposes was adopted. The convention also specifically requires that national agencies amounting in effect to monopolies shall be established or maintained for such cultivation wherever it is permitted.

Some of the principal provisions of the 1961 convention against the present treaty system were reviewed in the Commission and noted by the Council. The recommendatory embargo provisions of the International Opium Convention of 1925 were taken over in the new convention, with the extension that the new board may apply them against drug exporting countries as well as against drug importing countries. Also, the obligation to limit to medical or scientific purposes was extended to all narcotic drugs (including even such weak drugs as codeine and the so-called " exempted preparations "), whereas hitherto the use of some narcotic drugs, such as opium (other than medicinal opium), coca leaves and cannabis, had not been so restricted. The convention thus provides the culmination of the effort of over half a century in the agreement which was reached that after a definite transitional period all non-medical uses of narcotic

drugs (opium eating, opium smoking and the consumption of cannabis and coca leaves) would be outlawed everywhere, with a few temporary exceptions. The new convention would also require that all drugs and preparations be sold only by licensed vendors, whereas this requirement generally does not at present apply to raw opium, medicinal opium, cannabis, cannabis resin, extracts and tinctures of cannabis, exempted preparations, and to the retail trade in drugs in group II, and their preparations. The Council noted that two major propositions — mandatory prohibition of particularly dangerous drugs, and a closed list of opium producing countries — had not been adopted by the conference. Nevertheless, the new treaty provides that the prohibition of such drugs would be under a special type of recommendation. This has been the practice by the control organs hitherto, but has no express treaty basis.

The Council considered the two resolutions addressed to it by the conference, as annexed to its final act. The first invited the Council to examine at its thirty-second session the question of an increase in the membership of the Commission on Narcotic Drugs. The Council unanimously decided in resolution 845 (XXXII) to increase the membership to 21. The second invited the Council to study the possibility of taking measures which would ensure the rapid and smooth carrying out of the simplifications of the international control machinery. The Council was unanimous in its support of the principle of personal union between membership of the Permanent Central Opium Board and the Drug Supervisory Body, as envisaged in its earlier resolution 667 H (XXIV), and requested the Secretary-General to negotiate arrangements to that end with the organizations concerned. Finally the Council adopted, on the Commission's recommendation, a resolution [833 (XXXII)] recommending that the 1961 convention be studied as expeditiously as possible with a view to its early signature, ratification or accession, as the case may be.

Technical Assistance for Narcotics Control

Satisfaction was expressed both in the Commission and in the Council with the progress achieved in the field of technical assistance in 1960, this being the first year in the continuing programme of technical assistance in the field of narcotics control established by General Assembly resolution 1395 (XIV) since it came into effect. As regards country projects, ten fellowships were awarded to nine governments under General Assembly resolution 1395 (XIV), and three fellowships and the services of one expert were provided under the Expanded Programme of Technical Assistance. Some of these fellowships were in the laboratory of the United Nations Narcotic Drugs Division in the identification by physical and chemical means of the geographical origin of opium seized in illicit traffic; others were for members of the administrations and technical services controlling production, manufacture and distribution of drugs; others for police, gendarmerie, customs and excise and other enforcement officials; one was for an official from welfare services for after-care and rehabilitation and employment of addicts. Programmes of training were to be provided in twelve different countries or territories, and other governments have also expressed willingness to arrange programmes for training fellows.

As regards regional projects, under General Assembly resolution 1395 (XIV), a meeting of a consultative group on narcotics control for South-East Asia was organized in Bangkok in December 1960;* also a small amount of assistance was given at the request of several members of the Permanent Anti-Narcotics Bureau of the League of Arab States in respect of a conference which it organized on enforcement problems. The members of the Commission considered that the meeting of the South-East Asia group had been a most instructive experience, and expressed the hope that governments concerned would study carefully the suggestions made by the group.

Implementation of Treaties and International Control

In general, governments complied with their obligations under the various narcotics treaties to supply information and reports. During 1960, legislative texts on narcotic drugs for 61 countries and territories were communicated to the Secretary-General, and annual reports covering the year 1959 were received in respect of 134 countries and territories. The Secretary-General was requested to invite countries and territories that had not transmitted annual reports for two consecutive years to do so.

There was further progress during the last year towards adherence to the narcotics treaties. One more State had adhered to the 1948 protocol and one to the 1936 convention, the total ratifications or accessions in respect of the former being 58, and in respect of the latter 28.

Seven new drugs, six of them synthetic, were placed under international control during the last year. This brings the total number of basic narcotic drugs under control to 79, among them 51 synthetic drugs.

Illicit Traffic

In its annual review of the illicit traffic situation, the Commission was aided in its task by the Committee on Illicit Traffic and was also, as usual, assisted by observers from a number of governments and organizations. It gave attention to particular points regarding the illicit traffic, as follows: broad aspects of trafficking as a criminal pursuit and underlying principles of control; penal sanctions; prices of drugs on the illicit market; the use of air transport in the illicit traffic; international co-operation and intelligence work; salient features of the traffic in 1960. It was observed that a result of continually growing technological development and increased facility of communication was the increasing use of aircraft in the illicit traffic throughout the world. Co-operation among governments, strong national legislation, effective enforcement and adequate penalties were key-points for a programme against the illicit traffic.

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* A summary of the work of this group may be found on pp. 37-38.

Abuse of Drugs (Drug Addiction)

The Council noted that the Commission had reviewed the problem of drug addiction in its manifold aspects at its sixteenth session — its etiology, the economic and medical conditions under which it is likely to spread, the treatment of addiction both as a social problem and as a matter of dealing with individual addicts. It was recognized that the collection of accurate date of the number of addicts is extremely difficult — even approximate estimates are not easy to establish. An exact evaluation of the size of the problem would, however, be important for a comprehensive and effective approach to the question. The Commission considered that it would therefore be useful if some governments would supplement their normal methods of collecting data on drug addiction by special surveys.

Not only addiction to manufactured drugs continued on a large scale, but there was also a constant picture of heavy use of cannabis in almost all regions of the world, and in particular on the African continent, in large parts of the Middle East, and on the Indian-Pakistani sub-continent, as well as a continuing serious problem of coca-leaf chewing in some countries of South America. With respect to cannabis, the Council heard with interest that arrangements had been initiated to work more closely with African countries in respect of narcotic questions.

Opium and Opiates

Scientific Research

The United Nations Narcotics Laboratory concentrated its attention on the development of reproducible methods and on the analyses of authenticated samples, which were the basis for the investigation of seizures. The collection of authenticated opium samples in the United Nations laboratory increased, but there were still insufficient samples from certain regions, especially from South-East Asia and from Mexico, and also from some countries in the Middle East. Opinion was expressed in the Commission that the laboratory should also be provided with samples of opium produced illicitly. Technical assistance in the form of training had been given at the United Nations laboratory, and the Commission hoped that this work would be continued and possibly extended. The Commission agreed that in order to take advantage of recent advances in analytical chemistry, it seemed desirable that the laboratory should complete its present equipment and should have certain instruments, in particular an infra-red spectrophotometer and a fluorimeter, and expressed the hope that necessary budgetary arrangements could be made.

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